National Institute on Alcohol Abuse and Alcoholism

ALCOHOL AND BIRTH DEFECTS: THE FETAL ALCOHOL SYNDROME AND RELATED DISORDERS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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FOREWORD

In early 1977 the National Institute on Alcohol Abuse and Alcoholism (NIAAA) convened a workshop of scientific and medical experts from a variety of disciplines to examine the rapidly growing literature on alcohol and birth defects. After weighing the evidence that had been accumulating since the fetal alcohol syndrome was described by French investigators in 1968 and by American scientists in 1973, the workshop participants recommended that the NIAAA issue a statement about the risks to unborn babies when pregnant women drink heavily. The statement was issued in June 1977 by my predecessor, Ernest P. Noble, Director of the NIAAA.

Three years later, after publication of a special report[1] that reviewed newer findings on alcohol and birth defects, the Surgeon General issued an advisory reaffirming the NIAAA position of 1977 on heavy drinking during pregnancy. The Surgeon General further recommended that women who are pregnant or considering pregnancy avoid drinking altogether. This advice was based on evidence indicating that the effects of alcohol on the developing organism probably lie on a dose-dependent continuum—that the fetal alcohol syndrome in children of alcoholic women represents one end of the continuum, and that lower levels of drinking during pregnancy might also pose risks to the fetus, though to a lesser degree. Many health experts consider this a prudent recommendation that should be followed until research has demonstrated a safe level of drinking during pregnancy.

The National Institute on Alcohol Abuse and Alcoholism is proud of its role in fostering research and public education on this vitally important subject and is pleased to present this monograph, *Alcohol and Birth Defects: The Fetal Alcohol Syndrome and Related Disorders*, which reviews advances in the field. Since 1977, when the first NIAAA workshop on the fetal alcohol syndrome was convened, there has been enormous growth in our understanding of the effects of alcohol on the embryo and fetus. Structures in the developing brain that may be especially

[1] *Health Hazards Associated with Alcohol, and Methods to Inform the General Public of These Hazards*, published by the U.S. Department of Health and Human Services and the Department of the Treasury, 1980.

sensitive to alcohol are being identified, along with developmental stages of special vulnerability. Several factors that modify the risk of fetal damage from alcohol have also been found. Knowledge of the basic mechanisms of damage is growing. These and many other advances are discussed in the monograph, which is intended primarily for lay readers but will also be useful for health professionals who are not specialists in this area.

Enoch Gordis, M.D.,
Director
National Institute on
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Alcoholism

PREFACE

More than 15 years have passed since the publication of classic case reports describing infants displaying the constellation of alcohol-induced physical anomalies and mental retardation we now call the fetal alcohol syndrome, or FAS. It is now indisputable that alcohol is a teratogen—a producer of birth defects. In fact, alcohol is considered to be the leading cause of mental retardation arising from the action of known teratogenic agents.

The nature of the scientific literature on this subject has changed considerably since 1973, when the term *fetal alcohol syndrome* was coined by scientists at the University of Washington. The earliest reports were predominantly case studies describing the serious consequences of severe maternal alcoholism during pregnancy. Such reports continue to be published, of course, but the bulk of the scientific literature on FAS now deals with efforts to find answers to many questions about FAS and other conditions associated with maternal drinking during pregnancy:

How prevalent are FAS and less severe effects of alcohol consumption by pregnant women? Are FAS and fetal alcohol effects (FAE) becoming less prevalent as people become more aware of the risks, or has there been no change in their rates of occurrence in the population? Or are they perhaps becoming more prevalent, despite greater awareness of the risks?

What risks to the fetus are involved across the full range of possible maternal drinking levels? Pregnant women are now advised to avoid alcohol completely as a matter of simple prudence, but is there a threshold level of alcohol consumption during pregnancy, below which no harmful effects to the developing infant can occur? What are the consequences of low or moderate drinking during pregnancy?

What are the underlying mechanisms of FAS and FAE? Are there critical times during pregnancy when the risk is greatest? Are there tissues and organs in the developing infant that are especially vulnerable to alcohol? Can ways be found to protect the developing organism against alcohol damage? Can ways be found to reverse alcohol damage in the developing organism?

No population groups appear to be free of risk of FAS and related conditions, but are some groups more susceptible than others? And if so, why?

What are the most effective strategies for preventing FAS and fetal alcohol effects?

The search for answers to these and related questions is the subject of this monograph. The monograph reports considerable progress in finding answers to these important questions, but it also clearly indicates a need for continued research.

We are still a long way from knowing all we need to know about the effects of prenatal alcohol exposure—what they mean, how they occur, how they can be prevented, how they can be reversed. Further research will answer these questions. Recent research progress may have brought us to a state of knowledge at which the development of more coordinated and integrated research on FAS and FAE would be feasible and warranted. Increased coordination and integration would accelerate progress in understanding and dealing with the effects of prenatal alcohol exposure on development.

Knowledge of the risk is growing in our country, as documented in this monograph, and more pregnant women are abstaining from alcohol or greatly reducing their consumption. This monograph presents scientific evidence about the effects of alcohol on prenatal and postnatal development. Continuing research may allow us to identify the lower thresholds for fetal risk and answer key questions on therapeutic intervention, prevention, and reversal of fetal injury.

Several prominent investigators in the fetal alcohol field—Drs. Ann P. Streissguth, Sterling K. Clarren, Robert J. Sokol, and Carrie L. Randall—contributed significantly to this monograph by granting interviews for clarification of technical issues or by critically reviewing the manuscript. On behalf of the National Institute on Alcohol Abuse and Alcoholism, I thank all of them for their generous cooperation.

Kenneth Warren, Ph.D.
Director
Office of Scientific Affairs
National Institute on
Alcohol Abuse and
Alcoholism

INTRODUCTION

In 1970, Dr. Christie Ulleland, a young physician in her second year of a residency program in pediatrics at the University of Washington Health Sciences Center, Seattle, was studying the medical records of newborn infants whose weight at birth was abnormally low (Ulleland 1972). In the course of her investigation, she noticed four such newborns whose mothers were all alcoholics and drank heavily during pregnancy.

Further review of medical records yielded seven more such cases. Because of the strong association with maternal alcoholism, all 11 children were brought together for examination by Dr. David Smith, head of the dysmorphology (birth defects) unit at the Health Sciences Center, and his colleague Dr. Kenneth Jones. Smith and Jones were impressed by the similarity of these children, especially their facial features. All had short palpebral fissures, that is, their eye openings were abnormally small. Their upper eyelids drooped—a condition called ptosis. Their noses were short, creating a wide space above the upper lip, and the upper lip itself was very thin. The philtrum, the indentation in the skin that is normally present just above the upper lip, was reduced or missing. All the children were small for their age, their heads were abnormally small, and all were mentally retarded.

These discoveries led to the publication of a series of papers in the early 1970's by Ulleland, Smith, Jones, Streissguth, and others at the University of Washington (Ulleland 1972; Jones et al. 1973; Jones and Smith 1973; Jones et al. 1974), mostly in the British journal *Lancet*. Since that time, the term these investigators coined in their description of these congenitally deformed children has become familiar to millions of people around the world. The term is *fetal alcohol syndrome* or FAS, a cluster of severe congenital abnormalities of the head and face, as well as central nervous system damage, caused by heavy maternal drinking during pregnancy.

Since 1973, the fetal alcohol syndrome has become one of the most intensely studied areas in the field of alcohol research. The purpose of this monograph is to present an overview of the effects of alcohol on prenatal and postnatal development and to describe some of the significant research findings in this area that have been made in the past few years.

PREGNANCY AND ALCOHOL—A HISTORICAL OVERVIEW

Early Studies

The Seattle scientists were among the first to point out that, in identifying the fetal alcohol syndrome as a distinct clinical entity, they had not really discovered a new pathological condition associated with alcohol abuse. Actually, suspicion, as well as evidence, that alcohol could have harmful effects on unborn babies goes back a long way:

- In 1726, the British College of Physicians reported to the Parliament that parental drinking was "a cause of weak, feeble, and distempered children" (cited by Warner and Rosett 1975).
- In 1834, a commissioned report to the British House of Commons concluded that babies born to alcoholic mothers sometimes have a "starved, shriveled, and imperfect look" (cited by Jones and Smith 1973).
- Both in Britain and in the United States, numerous reports appeared throughout the 19th century describing the harmful effects of alcohol on offspring (cited by Rosett and Weiner 1984).
- The famous British scientist Sir Francis Galton noted (Galton 1899) that children of alcoholic mothers were healthy if they were born during periods of maternal sobriety, but were "neurotic" if they were born during periods of active maternal alcoholism. He reasoned that such children were born defective because "the woman's tissues must have been drenched with alcohol, and the unborn child alcoholized during all its existence in that state." Galton further reasoned that alcohol would diminish the quality of the mother's milk. He also recognized the contributing effect of a bad home environment created by an alcoholic mother, stating that the "surroundings of the home would be prejudiced to the health of a growing child."
- After Galton made these observations, W.C. Sullivan made what appears to be the first truly scientific study of the teratogenic (i.e., birth defect-producing) effects of alcohol (Sullivan 1899). Sullivan studied 120 chronic alco-

holic women incarcerated in the Liverpool jail, choosing his study group carefully so as to exclude cases of syphilis, tuberculosis, and degenerative disease that could confound the interpretation of his results. Of the 600 children born to these women, Sullivan found that 56 percent were either born dead or died before reaching the age of 2. This child death rate was 2-1/2 times higher than in a comparison group of 28 nonalcoholic female relatives of the alcoholic women. Sullivan also observed that the death rate among these children increased with the duration and severity of alcoholism in their mothers. The death rate among firstborn children of alcoholic mothers was 34 percent, but rose to 72 percent among sixth-born children. Likewise, the rate of stillbirths among alcoholic mothers increased from 6 percent for firstborn babies to 17 percent for sixth-born. Sullivan concluded that these increasing infant mortality rates among later births reflected the increasing chronicity and severity of alcoholism in the mothers. Perhaps his most dramatic observation, however, was that alcoholic women who had previously given birth to children with crippling or lethal birth defects later had healthy babies, apparently as a consequence of their forced abstinence from alcohol while in the Liverpool jail.

- In 1901, a French medical student named Paul LaDrague published his doctoral thesis (LaDrague 1901) presenting case reports suggesting that alcoholic mothers had high rates of spontaneous abortion, weak and poorly developed babies, high infant death rates, and high rates of epilepsy and mental retardation among their surviving children. LaDrague also described 10 cases in which infants breast-fed by alcoholic mothers or wet nurses experienced diarrhea, vomiting, extreme agitation, and convulsions. All the symptoms disappeared when the wet nurse or mother curtailed alcohol use.
- France was also the site of one of the first systematic studies on malformations in children of alcoholics. Again the report was a dissertation written by a medical student. The thesis, written by Jacqueline Rouquette (1957), presented evaluations of 100 foundling home children born to alcoholic

mothers and fathers. Rouquette described malformations associated with parental alcoholism that were very similar to those now recognized as part of the fetal alcohol syndrome. She found alcoholism in the mother to be especially threatening to the developing infant.

- In 1968, in Nantes, France, Dr. P. Lemoine and his colleagues (Lemoine et al. 1968) published their studies of 127 children born to alcoholic parents, mostly alcoholic mothers, and described a set of characteristics in the children that appeared to be related primarily to maternal alcoholism. The characteristics were practically identical to those described by the Seattle researchers a few years later. The French investigators were struck by the similarities among these children. They resembled each other so much that their appearance alone permitted a diagnosis of maternal alcoholism. Lemoine's paper was published in a journal of limited circulation, unfortunately, so it went largely unnoticed. Several years passed before it was even cited in the English language scientific literature.

The 20th Century Hiatus in Fetal Alcohol Research

Despite several early studies that supported the idea of birth defects associated with maternal alcoholism, articles on the subject dwindled and appeared only sporadically in the regular scientific literature during the first 50 years of the 20th century (Sokol 1982). What caused this lapse of interest? And what caused its resurgence in recent times?

Henry Rosett and Lyn Weiner in their recent book, *Alcohol and the Fetus: A Clinical Perspective* (Rosett and Weiner 1984) point out that, until recently, modern scientists have tended to discount early literature on this subject because much of it was based on flawed studies and tended to use moralistic and unscientific language. However, in the 13 years since Smith, Jones, and their colleagues published their key papers confirming that prenatal alcohol exposure can damage unborn babies, almost 2,000 articles on the fetal alcohol syndrome and related disorders have appeared in professional journals all over the world (figure 1). The willingness of the National Institute on Alcohol Abuse and Alcoholism to support research in this area no doubt played a role in the revival of interest in the effects of alcohol on prenatal development.

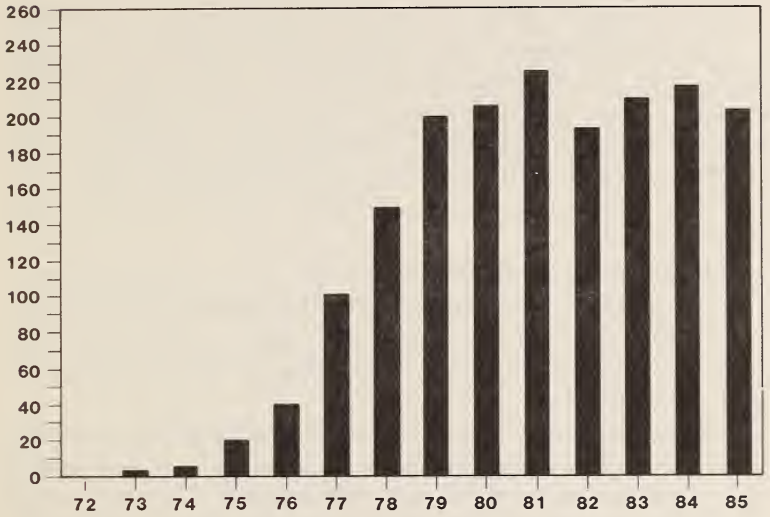

Figure 1.—Almost 2,000 publications on the fetal alcohol syndrome have appeared in scientific and medical journals since 1973, the year when descriptions of FAS as a distinct clinical entity were first published by dysmorphologists at the University of Washington. As shown in the graph, a very steep rise in publication rate occurred between 1973 and 1979. Since that time, the rate has remained fairly steady at around 200 per year.

SOURCE: Database of the National Clearinghouse for Alcohol Information.

The hundreds of case reports that have entered the medical literature from many countries since 1973, as well as confirmatory animal studies, leave no doubt that heavy alcohol consumption during pregnancy is associated with the risk of severe damage to unborn babies. The descriptions of the children in these reports are highly consistent with the classic picture drawn by the University of Washington scientists and their predecessors in France: characteristic cranial and facial deformities causing remarkable similarities in the facial features of the affected children, abnormalities in internal organ structure, central nervous system damage, and mental retardation—all associated with alcoholism in the mother during pregnancy.

DIAGNOSIS AND CHARACTERISTICS OF FAS

The Fetal Alcohol Study Group of the Research Society on Alcoholism recommended a standard set of diagnostic criteria (Rosett 1980), which were based on minimal criteria recommended earlier by Clarren and Smith (1978). The Study Group recommended that the diagnosis of FAS should be made only when a patient has one or more signs in each of the following three categories:

1. Prenatal or postnatal growth retardation.—Weight, length, or head circumference abnormally small for age.
2. Central nervous system involvement.—Signs of neurological abnormality, delayed development, or intellectual impairment.
3. Characteristic cranial and facial malformations.—At least two of the following signs: (a) abnormally small head; (b) small eyes or short palpebral fissures; (c) poorly developed philtrum, thin upper lip, or flattening of the cheekbones.

Retarded Growth

The most common sign of fetal alcohol syndrome is retarded growth in weight, length, and head circumference, both before birth and after (Rosett and Weiner 1984). The small size is not merely a reflection of premature birth, which some studies have shown to be associated with maternal alcohol use, because prematurely born FAS children are also smaller than premature non-FAS children of the same age. Furthermore, children born with FAS continue to show retarded growth even if they have adequate nourishment and are placed in a stable environment. In contrast to typical undernourished children, who show a growth spurt when their nutrition and environment improve, the children with FAS do not catch up.

Central Nervous System Effects

Another major characteristic of children with FAS is injury to the central nervous system, as indicated by mental retardation, poor ability to focus attention, delayed motor development, sleep disturbances, hyperactivity, and irritability. Several investigators have noticed that the children with the most severe central nervous system disorders seem to be the ones with the most

severe facial deformities (Streissguth et al. 1978; Majewski 1981). These investigators have also noticed that the degree of facial malformation is predictive of the patient's chances of improving; FAS children with severe facial deformities show little improvement in central nervous system functioning over time, but those with milder facial deformities tend to respond favorably to therapy and special training programs.

Cranial and Facial Anomalies

As noted in the Introduction, the facial malformations of children with FAS most often involve the eyes, nose, upper lip, and midface (Clarren 1981, 1982). The eyes are small (microophthalmia), sometimes crossed (strabismus), and near-sighted (myopia), and the eye openings (palpebral fissures) are narrow. The eyelids droop (ptosis), and epicanthal skin folds (diagonal folds of skin across the inner corners of the eyes, which are normal in many races but often a congenital anomaly in Caucasians) are sometimes present. The nose is typically short and upturned, and the nasal bridge is often reduced, giving the nose a flattened appearance at the top. The upper lip is thin and straight across the top (i.e., no "Cupid's bow"), and the abnormally wide area between the nose and the upper lip lacks a fully developed groove (philtrum). These features are diagramed in figure 2 and illustrated by photographs in figure 3. Also, some children with FAS may have bulging (or receding) foreheads, flattened cheekbones, underdeveloped lower jaws, or ears that are low-set and somewhat rotated. In addition to the facial malformations, other dysmorphology has been reported in association with FAS, including abnormalities in the urogenital system, heart, skeleton, and skin.

Which Facial Anomalies Are Truly Typical?

Although the facial features associated with FAS are what first drew attention to it, there is disagreement among experts as to which of the features described in the preceding paragraph are most typical of the syndrome. Clarren and Smith (1978) consider short palpebral fissures to be among the most characteristic features, but others disagree. Majewski, for example, considers the most typical facial characteristics to be the short upturned nose, the underdeveloped philtrum, and the thin upper lip (Majewski 1981).

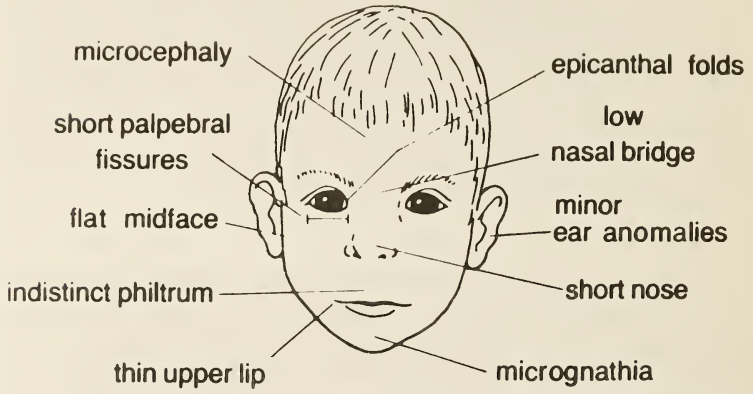

Figure 2.—Common facial characteristics of children with FAS. Features labeled on the left are seen frequently; those on the right are less specific to this syndrome.
SOURCE: Little and Streissguth 1982.

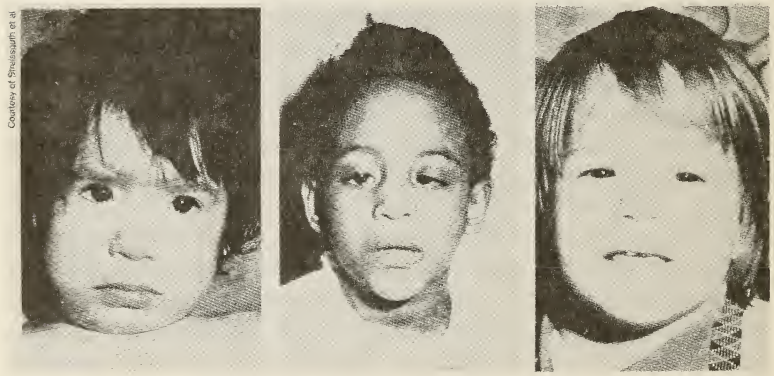

Figure 3.—Young children with FAS. Several common facial features of FAS are visible, including indistinct philtrum, short palpebral fissures, epicanthal folds, and low nasal bridge.
SOURCE: Jones et al. 1973.

It is interesting that experts who can disagree over what are the most "typical" facial features in the fetal alcohol syndrome nevertheless agree that the facial aspect, taken as a whole, is highly diagnostic. Thus Majewski (1981), after studying more than 100 patients with fetal alcohol damage, stated that their facial features "are so typical that diagnosis of maternal alcohol-

ism in almost all cases is possible from the aspect of the children alone." And Clarren and Smith stated (1978) that "taken as a whole, the face of patients with the fetal alcohol syndrome is as distinctive as that of patients with the Down syndrome...." However, Clarren and Smith also acknowledged that a trained eye is important in diagnosing the fetal alcohol syndrome. This has suggested to one reviewer (Abel 1983) that many cases of fetal alcohol syndrome must therefore be going undetected, because eyes trained to spot the syndrome are not abundant.

The Original FAS Children 10 Years Later

In 1983, 10 years after the University of Washington scientists first published their descriptions of 11 FAS children in *Lancet*, Streissguth and her colleagues at the University of Washington (Streissguth et al. 1985) reexamined as many of these children as they could find to determine how they had fared over the years. Two of the original group had died and one could not be located, leaving only eight available for reexamination. The findings of this followup indicate the lasting consequences of heavy maternal alcohol consumption during pregnancy.

Of the eight children, several of whom are now in their teens, four are in the borderline-retarded to low-normal range of intelligence (IQ 70 to 86) but have attended regular classes supplemented with remedial education. The other four, with IQs ranging from 20 to 57, are severely retarded and have had to be in special classes. An earlier followup study of these children when they were much younger noted that the degree of intellectual impairment was correlated with the severity of malformation and growth deficiency (Streissguth et al. 1978). This correlation has persisted.

The physical characteristics of these eight children remain similar to those initially reported in 1973, although facial appearances have been altered somewhat by increased growth of the chin and nose. Characteristic FAS facial features such as short palpebral fissures, strabismus, epicanthal folds, ptosis, underdeveloped philtrum, and flat midface have persisted. All the children remain below average in height and head circumference. Although there has been improved weight gain with age, the adolescent girls have a short, stocky stature and the adolescent boys tend to be short and lean.

A number of new physical problems are evident that were not observed in the initial studies. These include chronic middle ear infections with sustained hearing loss, severe dental malocclusions, and vision problems. Although cardiac defects were found in most of these children in 1973, they have not been a major medical problem.

Two of the children continue to live with their natural mothers. The mothers of three children, who were among the four most severely handicapped, died of alcoholism within 6 years after the children were born, which suggests to these investigators that biological factors associated with the terminal stages of alcoholism may have contributed to the severe handicaps in these children. Two of the most severely handicapped children lived in the most stable foster homes, which leads the investigators to suggest that the quality of the later home environment does not ameliorate the damage caused by prenatal alcohol exposure. However, stable home environments did produce improvements in social and emotional development.

THE FREQUENCY OF ALCOHOL-RELATED BIRTH DEFECTS

Incidence of FAS

From the hundreds of case reports of FAS in the literature, it is clear that the mothers of the affected children were all chronic alcoholics who drank heavily throughout pregnancy. No cases of FAS have been reported in the children of women who drank moderately. Some investigators have surveyed worldwide case reports to make rough estimates of the chances of a pregnant alcoholic woman having a baby with FAS. However, even if recognized by a trained observer, not every case of FAS will appear in the literature as a case report.

Prospective, or longitudinal, studies have provided more reliable figures on the incidence of FAS (that is, the rate of appearance of new cases). Greater reliability in such studies arises from the fact that diagnostic criteria for FAS are more rigorously defined and are applied uniformly by the same group of investigators, and the studies involve surveillance of a defined population over time. Incidence figures from such studies have varied depending on the location and the population investigated. Estimates for U.S. cities have ranged from 0.4 per 1,000 live births in Cleveland (Sokol et al. 1980) to 1.3 per 1,000 in Seattle (Hanson et al. 1978) to 2.1 per 1,000 in Boston (Rosett et al. 1983) to 3.3 per 1,000 in a later Boston study (Ouelette et al. 1977). Estimates from Europe range from 1.4 per 1,000 in France (Dehaene et al. 1981) to 1.6 per 1,000 in Sweden (Olegard et al. 1979).

A common estimate for overall incidence of FAS, 1 to 3 per 1,000 live births, is based on several reports (Dehaene et al. 1977; Hanson et al. 1978; Olegard et al. 1979; Rosett et al. 1983; Sokol et al. 1980). Based on this estimate, the number of FAS births in this country each year would be 3,600 to 10,000.

There is also evidence that certain subgroups in the population have a much higher incidence of FAS than the 1 to 3 per 1,000 estimated for the general population. A recent epidemiological study of southwestern American Indian populations, for example, found that certain tribes of the Plains Culture have the highest incidence of FAS so far recorded—9.8 cases per 1,000 live births, about 1 FAS per 100 births (May et al. 1983).

Partial Manifestations of FAS Signs—Fetal Alcohol Effects

A diagnosis of FAS is usually made only when a child has features in three main areas: growth deficiency, central nervous system dysfunction, and craniofacial anomalies (Clarren 1982). However, there are many cases where the children of heavy-drinking or alcoholic women show only some of these signs. In clinical practice, consequences of maternal alcohol use that do not meet the full criteria of FAS are often placed in the category of suspected fetal alcohol effects (FAE). Low birthweight, for example, can be a fetal alcohol effect (Rosett and Weiner 1984). However, many other factors can also cause reduced birthweight. Though it is possible to measure the degree to which alcohol consumption levels increase the incidence of low birthweight in a population, a clinician may suspect but cannot say with any confidence that a particular infant's low birthweight was caused by alcohol.

The uncertainties surrounding any diagnosis of a fetal alcohol effect make it difficult, but not impossible, to estimate the incidence of such effects in the population as a whole. As with many other disorders studied by epidemiologists, it is reasonable to think that individuals with the full fetal alcohol syndrome are probably far outnumbered by less severe cases. Dr. Robert Sokol, an obstetrician/gynecologist who specializes in perinatal medicine at Wayne State University School of Medicine, Detroit, has estimated that approximately 5 percent of all birth defects could be associated with prenatal alcohol exposure (Sokol 1981).

Thus the picture now emerging is that prenatal damage from alcohol is not an all-or-nothing phenomenon. Instead, most experts in the field now believe that alcohol's effects on the embryo and fetus show dose-dependent gradations. The alterations caused by alcohol are believed to lie on a continuum. They may range from subtle behavioral and neurological abnormalities (reflecting minor effects on the central nervous system during development), to a partial display of physical malformations that resemble those of FAS and may (with some uncertainty) be attributed to drinking during pregnancy, to the full cluster of severe anomalies seen in the offspring of women who are alcoholics.

EFFECTS OF MATERNAL DRINKING AT LOWER LEVELS

The rediscovery of FAS raised questions about how much alcohol a woman can safely consume during pregnancy; indeed, whether any level is safe; and whether drinking is riskier at some phases of pregnancy than at others.

The key issues are the relationship between dose and response and the timing of the dose. As with all pharmacological substances, alcohol's effects on the body vary according to dosage. Thus, a single drink can produce a sense of relaxation; for some, a few more can generate conviviality; several more can produce stupor; too many can cause heart failure, respiratory arrest, and death. Similar dose-response relationships are seen in all aspects of alcohol consumption, including gradations of liver, heart, and brain damage in the case of chronic alcohol abuse.

Because of this general principle of pharmacology and toxicology, alcohol researchers have good reason to suspect that the highly visible full FAS may be only the extreme of a continuum of effects from prenatal alcohol exposure. But proving that a broad range of dose-dependent hazards exists for the children of women who drink during pregnancy is much harder than demonstrating the existence of the full FAS in the children of female alcoholics.

The women who have given birth to babies with the unmistakable characteristics of FAS have been clearly alcoholic, drinking very large amounts during their pregnancies and in some cases suffering from alcohol-related disorders such as liver disease. Discerning relationships between effects and their probable cause is fairly straightforward in such extreme cases: one notices a cluster of striking abnormalities shared by a group of babies or young children; then one notices that every single one of their mothers is an alcoholic who drank heavily throughout her pregnancy; then one notices that this particular clustering of abnormalities is never seen in the children of nonalcoholic mothers. In these situations it is not difficult to conclude that maternal alcoholism is the probable cause of the birth defects, or at least is strongly associated with them. Replicating these effects by giving pregnant animals alcohol, under conditions that rigorously control for other possible risk factors, practically settles the question: alcohol is the most probable cause.

The problem with these obvious cases of FAS linked to obvious maternal alcoholism is that they can yield no information about the relative risk of alcohol-related injury to the fetus at lower levels of maternal drinking. The mothers of children with FAS all drink heavily, but extrapolating from that to lower levels of consumption is like trying to construct a graph with only one point. What is needed is a dose-response curve to measure the developmental effects of maternal drinking at every level from the lowest to the highest.

It is extremely important to understand the full spectrum of alcohol's effects at every stage of embryonic and fetal development and at every level of maternal drinking, including social drinking. *Especially* social drinking; it is so common that any deleterious effects it may cause in offspring, however mild or infrequent, could constitute a significant public health problem in the aggregate because of the sheer numbers involved.

Longitudinal Studies

Because the effects on the fetus of lower levels of maternal drinking are likely to be subtle and relatively infrequent, a special kind of epidemiological investigation, called a longitudinal or prospective study, is required to detect them. In such a study, the characteristics of individual women in a study population are assessed at some early time; then followup studies are made on their babies over a period of several months or years to see if any effects in the children can be statistically correlated with certain characteristics in the mothers. Unlike the study of babies with FAS and their alcoholic mothers, the subjects in longitudinal studies are not selected because they stand out as abnormal. Instead they are a sizable number of individuals, in this case, pregnant women who (ideally) are representative of the general population of pregnant women to the greatest extent possible.

If a study population of pregnant women is fully representative, one could expect to find the full range of drinking patterns, from occasional and light social drinking to heavy drinking and alcoholism, as in the general population of pregnant women and in the same proportions. A large study population increases the sensitivity of a longitudinal study in detecting infrequent abnormalities and in achieving statistical significance for measurements that deviate only slightly from normal. There are practical

limits to the size of a study population, though, and the main one is economic.

Longitudinal studies on pregnant women and their offspring are underway in various parts of the world, including some in the United States that are funded by the National Institute on Alcohol Abuse and Alcoholism.

The Seattle Longitudinal Study on Alcohol and Pregnancy

This study is a component of the Seattle Pregnancy and Health Study, which is the oldest continuing study of factors that may affect pregnancy outcome. The main purpose of the Alcohol and Pregnancy study is to evaluate the long-term effects of prenatal alcohol exposure on the growth and development of infants and children, although a variety of other factors including nicotine and caffeine intake are also measured.

It is essential to have data on maternal smoking and the use of other drugs besides alcohol in order to determine the independent effects of alcohol and these other potential risk factors. For example, although congenital birth defects have been clearly associated with maternal drinking during pregnancy but not with maternal smoking, both practices are known to cause low birthweight.

A total of 1,529 predominantly white, married, and middle-class women in prenatal care were interviewed about their alcohol, tobacco, and drug use, and a cohort of about 500 children born to these mothers was selected for followup studies spanning a period of 7 years. The mothers of the selected children were classified on the basis of their self-reported quantity and frequency of alcohol consumption during an interview in the fifth month of pregnancy. Among these women, drinking levels during the previous months ranged from total abstention to heavy drinking. The followup protocol for the children included examination within the first 2 days of birth, at 8 and 18 months, and at 4 and 7 years of age.

Analysis of test data obtained on these children at 4 years of age was recently completed. The analysis demonstrated several neurological and behavioral effects in children whose mothers consumed alcohol either lightly, moderately, or fairly heavily during pregnancy. Neurological and behavioral effects in these

children were measurable from the first day of life at all three levels of maternal drinking, have persisted until at least 4 years of age, and on several measures are proportional to the amount of alcohol their mothers consumed while pregnant. Furthermore, the data gathered so far do not suggest a "threshold" level of alcohol consumption below which no effect on the unborn child can occur. However, it must be noted that the observed effects are relatively small and their clinical significance is still hard to assess. Details of these findings are presented below.

Effects of Prenatal Alcohol Exposure in Newborns

Habituation. One of the tests given to the infants shortly after birth measures a behavioral characteristic called habituation. This is the ability to "tune out" and stop responding to an extraneous stimulation. The Seattle researchers have found that habituation to a repeated stimulation in newborns is strongly related to the amount of maternal drinking during pregnancy. The more alcohol the mothers consumed while they were pregnant, the longer it took their babies to become habituated to a repeated stimulation and stop responding to it (Streissguth, Martin et al. 1983). The importance of this discovery is that delayed habituation in infancy can be an indicator of delayed central nervous system development (Lewis 1975).

Sucking Reflex. Two tests were used to measure the sucking reflex, which of course is directly related to the ability of infants to take in nutrients. The investigators found that maternal alcohol consumption during pregnancy impairs the sucking reflex of babies (Martin et al. 1979). The time it takes for a baby to start sucking when presented with a stimulus that normally provokes it was significantly prolonged by maternal drinking, and the more the mother drank, the longer the delay. Strength of sucking also was significantly reduced in the babies of women who drank during pregnancy, and again the degree of decrement was related to the amount of alcohol the mother had consumed.

Other Newborn Behaviors. Five other behaviors in newborns were found to be significantly related to alcohol exposure during pregnancy (Landesman-Dwyer et al. 1978). Babies of mothers who drank while pregnant showed alcohol dose-response relationships in three of these behaviors: significantly increased body tremors, a greater tendency to turn the head to the left (which is not typical for full-term babies), and a decrease

in vigorous bodily activity. Two other behavioral differences—greater amount of time spent with the eyes open and greater hand-to-face activity—were seen only in the babies of mothers who drank more heavily and therefore cannot be interpreted in terms of a dose-response relationship.

Data on habituation, sucking reflex, and other newborn behaviors are summarized in figures 4 and 5.

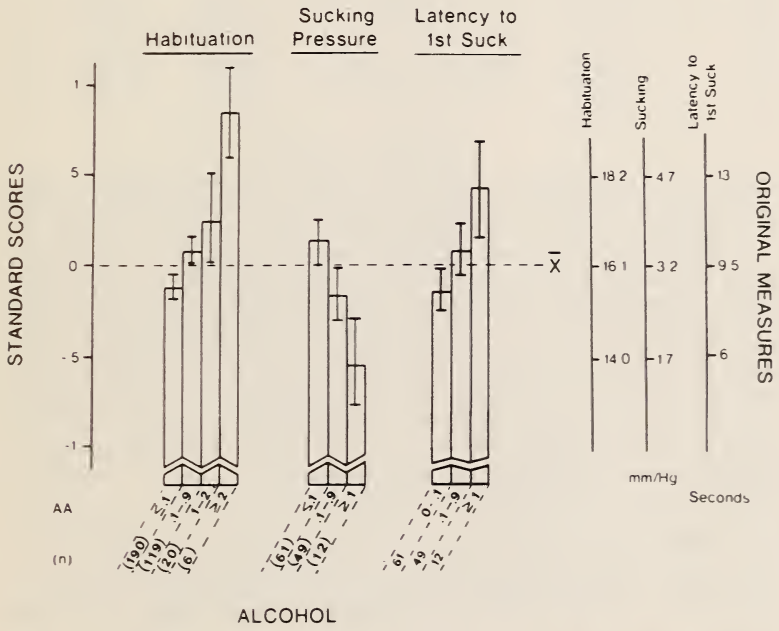

Figure 4.—Habituation and sucking scores for infants of mothers reporting different levels of alcohol use in pregnancy (scores adjusted for such variables as maternal smoking and caffeine use during pregnancy as well as gestational age, parity, and maternal education). Note the nearly linear relationship between delayed habituation in infants and increasing average daily levels of maternal consumption of alcohol during pregnancy, ranging from less than 0.1 ounce of absolute alcohol to more than 2 ounces a day (values labeled AA at the bottom of the graph). A similar proportionality was found in measurements of the sucking reflex. The graph in the middle shows a nearly linear decline in sucking strength with increasing levels of maternal drinking. The graph at the right shows a linear relationship between levels of maternal drinking and the time it takes infants to begin sucking when presented with an appropriate stimulus.

SOURCE: Streissguth, Barr, and Martin 1984.

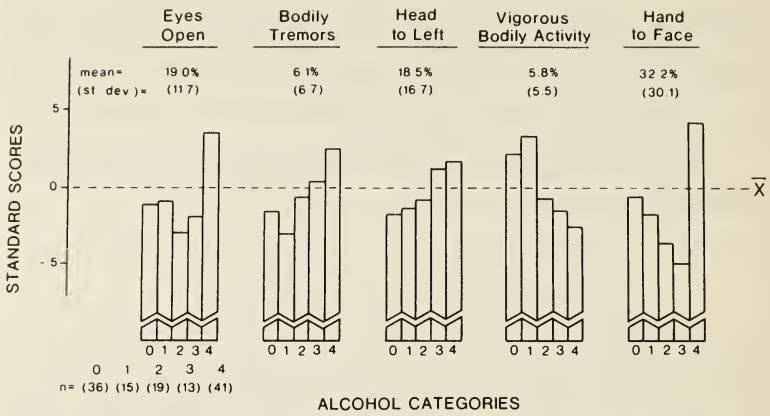

Figure 5.—Observations of newborn infants in relation to different levels of maternal alcohol use in pregnancy (scores adjusted for such variables as maternal smoking and caffeine use during pregnancy as well as gestational age, parity, and maternal education). Height of the bars is proportional to the amount of time the infants of mothers in the different alcohol use categories engaged in various behaviors. Maternal alcohol use ranged from none to heavy (0 to 4 at the bottom of the graphs). Greater amount of time spent with eyes open (left graph) and greater hand-to-face activity (right graph) were seen only in the babies of mothers who drank more heavily. However, proportionality with maternal drinking levels was seen in amount of body tremors, tendency to turn the head to the left, and less vigorous body activity (middle three graphs).
SOURCE: Streissguth, Barr, and Martin 1984.

Effects of Prenatal Alcohol Exposure in Older Babies

Mental and Motor Development. Measurements with standard psychological tests at 8 months of age have shown a statistically significant delay of mental and motor development in the babies of women who drank during pregnancy (Streissguth, Barr, Martin, and Herman 1980). The degree of decrement in both categories of development was related to the amount of alcohol the women had consumed, but mental development in the babies was found to be disproportionately reduced at the higher levels of maternal alcohol consumption (figure 6).

Effects of Prenatal Alcohol Exposure at 4 Years of Age

Attentional Deficits. The Seattle study has found that 4-year-old children whose mothers were heavier drinkers during pregnancy show clear decrements in the ability to perform tasks that require vigilance and fast reaction (Streissguth, Barr, and

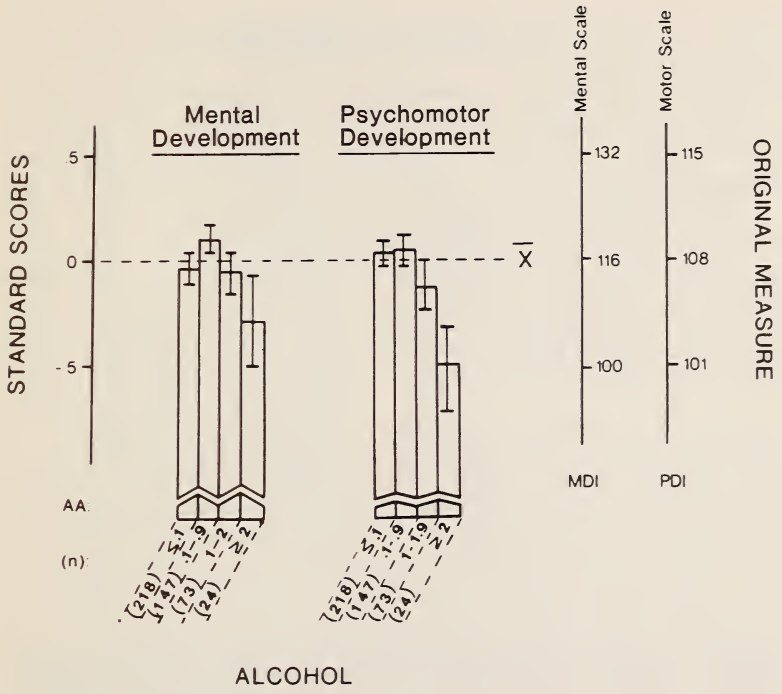

Figure 6.—Scores for mental (left) and psychomotor development (right) in infants of mothers reporting different levels of alcohol use (AA) during pregnancy (adjusted for such variables as maternal smoking and caffeine use during pregnancy as well as gestational age, parity, and maternal education). Measurements were made at 8 months of age. Both mental and psychomotor development in infants show a decline with increasing levels of maternal drinking.

SOURCE: Streissguth, Barr, and Martin 1984.

Martin 1984). In the test, which requires sustained attention and timely pressing of a button in response to a visual stimulus, 4-year-olds who received the greatest exposure to alcohol in utero showed the greatest deficits. They made significantly more errors of omission (failing to press the button when the stimulus was present) and more errors of commission (pressing the button when no stimulus was present) (figure 7). The attentional deficit was judged to be not simply a consequence of hyperactivity, because the most highly exposed children, who were the poorest performers on this test, did not differ from the other children in their overall orientation to the display board or in their activity

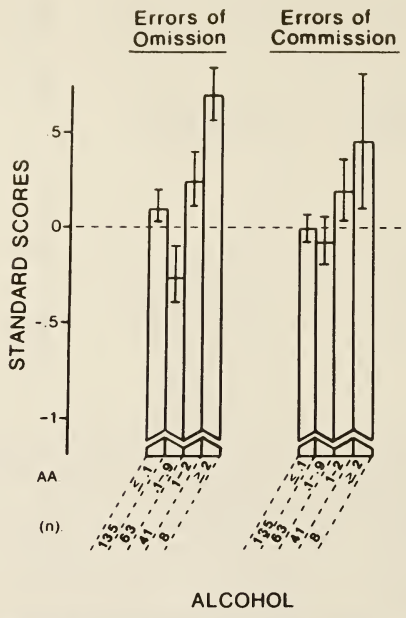

Figure 7.—Attention scores for 4-year-old children of mothers reporting different levels of alcohol use (AA) during pregnancy (adjusted statistically for maternal nicotine, caffeine, and nutrition during pregnancy, as well as maternal education, and parity). Errors of omission and commission in a vigilance task increased with increasing levels of maternal drinking.

SOURCE: Streissguth, Barr, and Martin 1984.

level during testing. The demonstration of attentional decrements in these 4-year-old children of the women who drank more heavily is an important finding, and a subsequent study has shown similar attentional deficits in these same children at 7 years of age (Streissguth et al. in press). The investigators suggest that subtle attentional deficits found in clinically normal children may lie on the same continuum as the attentional/activity disorder that often characterizes patients with FAS.

Clinical Findings at 4 Years

While the research cited above deals with subtle central nervous system effects associated with prenatal alcohol exposure in large groups of children, most of the children studied were not clinically abnormal when examined individually. Streissguth,

Barr, and Martin (1984) also examined prenatal alcohol exposure in terms of clinical ratings of "suspect or abnormal" at 4 years of age, based on a 2-1/2-hour psychological and anthropomorphic examination of this cohort. The risk of having a child who is clinically suspect or abnormal at 4 years of age appears to be increased only if a pregnant woman consumes, on average, the beverage equivalent of two ounces or more of absolute alcohol a day (i.e., four standard drinks [1]). However, the more sensitive laboratory tests continue to show slower information processing and reduced attention even in children prenatally exposed to lower levels of alcohol. Whether these deficits will persist and affect performance in school will not be known until the 7-year followup study is concluded.

The Seattle researchers caution that their study necessarily groups a variety of possible drinking patterns together in the same average daily consumption categories, and that some of the drinking patterns within each level of average daily drinking may be riskier than others (Streissguth, Barr, and Martin 1984). For example, moderate-to-heavy drinking episodes alternating with periods of abstinence could produce the same average daily alcohol consumption as daily light drinking at a constant level, or even a lower daily average, but the episodic drinking pattern might be more damaging to the embryo or fetus if the heavier drinking happens to coincide with the most critical stages of development.

Further, as noted above, the neurological and behavioral effects found associated with low to moderately heavy maternal alcohol consumption during pregnancy are relatively small, and measurements in large numbers of children were required to reveal them in statistically significant ways. This makes it hard to assess their significance for individual cases (Streissguth, Barr, and Martin 1984).

Finally, it should be noted that this study, as well as other prospective human studies of alcohol-related effects in pregnancy to date, have had to rely on the subjects' self-reported

[1] A standard drink is 12 ounces of beer, 5 ounces of wine, or 1-1/2 ounces of 80-proof distilled spirits (whether served straight or diluted with a mixer such as ginger ale or club soda). In these quantities, all three beverages have about the same alcohol content, i.e., slightly more than half an ounce of absolute (pure) alcohol.

drinking behavior. The development of biomedical indicators to quantitate objectively the amount of drinking would help corroborate the drinking information supplied by the subjects and would permit better comparisons between different studies. As shown below, not all prospective studies of alcohol and pregnancy have found subtle behavioral effects associated with nonalcoholic drinking levels.

The Ottawa Prenatal Prospective Study

Adverse effects of "social" levels of drinking during pregnancy were reported in a recent Canadian study (Gusella and Fried 1984) of middle- to upper-middle-class women and their babies. The study was part of the Ottawa Prenatal Prospective Study which, since 1978, has been examining the relationship between maternal lifestyles during pregnancy and infant development. The social drinking study involved a much smaller sample than the Seattle study. The investigators studied a group of 84 consecutively selected mothers whose average daily consumption of alcohol during pregnancy, expressed as standard drinks, was 44 percent, 37 percent, and 33 percent of a standard drink in the first, second, and third trimesters respectively. During the first trimester, 33 percent of the women drank between .25 of a standard drink and 1.6 standard drinks a day, and 7 percent drank more than 1.6 drinks a day. By the third trimester 39 percent drank between .25 of a standard drink and 1.6 standard drinks a day, and 1 percent consumed more than 1.6 standard drinks a day. Only one woman consumed an average of more than 2.8 drinks a day throughout pregnancy. Binge drinking was so infrequent in these women that it was not treated as a separate variable.

Developmental performance in the 84 offspring of these mothers was measured at 13 months of age using a standard test battery that measures sensory perception, memory, problem solving, vocalization, gross and fine motor movement, attitude, interests, and temperament. The tests were administered to the infants by an examiner who had no knowledge of the mothers' prenatal drinking and smoking habits.

Results suggested that "social" drinking during pregnancy was associated with lower scores on tests of spoken language and verbal comprehension. Maternal smoking was found to be

related to decreased motor functions and decreased verbal comprehension. While these results suggest that drinking at social levels or smoking during pregnancy might have adverse effects on the offspring, the clinical significance of the findings will not be known until long-term followup studies are made.

The Cleveland Fetal Alcohol Study

Effects of lower levels of maternal drinking have also been examined in the Cleveland Fetal Alcohol Study (Ernhart et al. 1985). Fetal alcohol effects examined included specific physical anomalies, intrauterine growth retardation, and neurobehavioral deficits. This study examined 359 infants born to disadvantaged women, 176 of whom scored positive on the Michigan Alcoholism Screening Test (MAST), which measures history of alcohol abuse but not necessarily current drinking, and 183 of whom were MAST-negative. Assessments of these newborns included a tally of alcohol-related physical anomalies; measurements of weight, length, and head circumference; and neurobehavioral testing.

This study did not detect the neurobehavioral decrements seen in the Seattle and Ottawa studies, but it did identify some maternal drinking factors that affected the incidence of physical anomalies in the offspring. The number of physical anomalies was greater in the infants whose mothers had a history of alcohol abuse before pregnancy and was highest in those who were MAST-positive and also had higher alcohol consumption levels during the first trimester. Persistent exposure to alcohol, at least in the first trimester, was the crucial factor in determining increased occurrence of physical anomalies.

Intrauterine growth deficiency was associated with being black, having smaller parents, and being female, but was independent of both earlier history of alcohol abuse in the mothers and their alcohol consumption during pregnancy. Ernhart and colleagues point out that, though size effects are clearly a feature of FAS, they have not been consistently obtained in all studies of lower levels of alcohol exposure, perhaps because of "reasonable fluctuations of a small, but true, effect being assessed at or near threshold."

FACTORS DETERMINING SUSCEPTIBILITY TO PRENATAL ALCOHOL EFFECTS

The frequency of FAS and alcohol-related birth defects is much lower than the frequency of abusive drinking among pregnant women. This finding is clearly shown in longitudinal studies. In the first Cleveland Fetal Alcohol Study, for example, only 5 babies among the 204 offspring of heavily drinking women had FAS, and no more than half of the 204 infants had any abnormality that could be attributed to prenatal alcohol exposure (Sokol et al. 1980). A similar difference between rates of heavy prenatal alcohol exposure and adverse pregnancy outcome is also evident in data on infant neurobehavioral development from the Pregnancy and Health Study in Seattle. In that study, the investigators found that 19 percent of the 4-year-old children born to mothers reported consuming an average of 2 or more ounces of absolute alcohol per day (four standard drinks) during pregnancy were rated clinically abnormal or suspect after an extensive clinical examination (Streissguth, Barr, and Martin 1984).

These figures suggest that the impact of alcohol on prenatal development is modified by other factors. What these other factors are is a matter of great interest from a public health standpoint, because this knowledge would allow more intense prevention efforts to be directed to the individuals or populations at greatest risk.

Although published literature on the question of what affects prenatal susceptibility to alcohol damage is very sparse, a number of factors might explain why only some infants are harmed by heavy maternal drinking during pregnancy. Some embryos and fetuses may be genetically more susceptible to alcohol damage than others. There may be variable maternal factors that have a protective effect. Fetal or embryonic damage may be enhanced by other risk factors that work synergistically with alcohol. Varying susceptibility may also be related to specific drinking patterns and peak blood alcohol levels attained, the effects of which have not yet been fully characterized.

The possible existence of modifying factors has recently been examined by investigators at the Cleveland Fetal Alcohol study (Sokol et al. in press). Their study examined modifying

factors in two areas: intrauterine growth retardation and the full fetal alcohol syndrome.

Factors Modifying Alcohol-Related Growth Retardation

To identify factors that might modify the risk of low birthweight, the most consistently reported effect of prenatal alcohol exposure, scientists reexamined data from 5,093 pregnancies that had been obtained in an early NIAAA-sponsored prospective study at Loma Linda University. Of 44 potential determinants of birthweight examined, 10 were found to contribute significantly and independently to intrauterine growth retardation (Kuzma and Sokol 1982). The type of beverage chronically consumed was found to be an important determinant of risk. Specifically, chronic beer consumption during pregnancy was found to be one of the most significant contributing factors to alcohol-induced growth retardation. An alcohol-related birth decrement of about 100 grams was seen only in the 176 pregnancies (3 percent) in which the mother consumed beer more than 20 days a month. Further analysis of these 176 pregnancies (in comparison with 149 other pregnancies that yielded infants with greater weight) revealed several additional factors that contributed independently to low birthweight among the chronic beer drinkers: these mothers were also more likely to be black (26 percent vs. 7 percent), more likely to have weighed 11 pounds less before they became pregnant, and more likely to have gained an average of 5 fewer pounds during pregnancy.

Further analysis of 2,233 pregnancies in which the mothers drank any amount of beer also revealed that growth retardation was associated with lower maternal weight before pregnancy, lower weight gain during pregnancy, ethnicity, and frequent beer drinking, as well as cigarette smoking. These associations were highly significant statistically.

Each of these factors also appeared to operate independently of the others; that is, they were additive. It is possible, however, that abusive drinking might interact synergistically (more than additively) with other risks that were not measured in this study—genetic predisposition, for example. The investigators found no factors that ameliorate the significant growth-retarding effect of alcohol on the fetus, indicating that alcohol abuse should continue to be regarded as a risk in any pregnancy.

Factors Modifying Risk of FAS

To examine contributory risk factors for the full FAS, Sokol and colleagues (in press) used data from their own ongoing NIAAA-supported Cleveland Fetal Alcohol Study. The data base in this study consists of information gathered over a 33-month period on 8,331 consecutive pregnancies and includes patient identification, MAST scores, self-reported daily alcohol intake during the preceding 2 weeks, nutrition, other drug use, and medical and obstetric information.

From the approximately 11 percent of these women who scored positive on the MAST test (that is, had a history of alcohol problems), a group of 600 was recruited for study and matched for 7 factors with 600 MAST-negative women. The newborn infants of all 1,200 women were then examined for alcohol-related birth defects by investigators who were unaware of the mothers' MAST scores and their drinking levels and patterns during the recently completed pregnancy.

Twenty-five cases of FAS were identified (an FAS rate of approximately 3 cases per 1,000 live births in this population). These 25 babies were matched with 50 non-FAS control infants to examine the issue of susceptibility to FAS. Statistical analysis of data from the two groups of infants and their parents revealed no differences in socioeconomic status, educational level, cigarette smoking, narcotic use, prepregnancy weight, nutrition, obstetric risk score, previous abortions, or father's weight. However, FAS was associated with increased maternal age, increased frequency of black race, greater number of previous pregnancies, higher frequency of MAST positivity, greater proportion of drinking days, greater consumption of alcohol per drinking day, and greater proportion of alcohol from beer (Sokol et al. in press).

Four of these variables accounted for nearly two-thirds of the variance in FAS/non-FAS outcomes: percentage of drinking days, MAST test scores, number of previous births, and race. Analysis revealed that if none of these four risks is present the probability of the infant having FAS is less than 2 percent. If all four are present (that is, high percentage of drinking days, positive MAST score, high number of previous births, and black race) the probability of the baby being born with FAS rises to 85.2 percent, a more than fiftyfold increase in probability.

These studies found that black race may be an important susceptibility factor both for alcohol-induced growth retardation and for the full FAS. The first study (Kuzma and Sokol 1982) found that black race and frequent beer drinking additively increase the chances of low birthweight for gestational age. The second study (Sokol et al. in press) found that black race considerably increases the risk for FAS. This finding is consistent with a recent report by Iosub and colleagues (1985) in which a comparison of the incidence of FAS in blacks and Hispanics revealed that single and multiple cases of FAS are more frequent in blacks.

Although these studies indicate that race may influence susceptibility to FAS, it is crucial to note that numerous studies around the world involving many ethnic and racial groups have shown that none is immune.

Sokol and his colleagues (in press) conclude that factors that may modify the susceptibility of the fetus to alcohol teratogenicity have not been adequately studied in the past, that much more research is needed in this area, and that studies of the impact of alcohol on human pregnancy outcome, particularly those related to neurobehavioral development, would do well to focus on factors that may additively or interactively modify the impact of alcohol on offspring.

FAS STUDIES IN ANIMALS

Animal models play a very important role in the study of fetal alcohol effects and FAS because they allow those effects to be examined under carefully controlled conditions that are impossible to achieve with humans. Many of the physical features of FAE and FAS, as well as several behavioral ones, have been reproduced in experimental animals, thus confirming the causative role of alcohol.

Demonstration of Alcohol Teratogenicity

An association between maternal alcoholism and birth defects does not in itself prove that one phenomenon actually causes the other, though it certainly can create a powerful suspicion. But alcoholism is a very complex disease that frequently is accompanied by malnutrition, deranged metabolism, other drug use, heavy smoking, poor general health, damage to vital organs, increased susceptibility to infection, and disinclination or inability to obtain proper prenatal care. Any of these associated factors, either singly or in combination, conceivably could damage the embryo or fetus at crucial stages of development and therefore might explain the birth defects associated with maternal alcoholism.

Thus, one of the earliest and most urgent scientific questions to arise after the discovery of FAS was this: What actually causes the birth defects? A toxic effect of alcohol itself on the embryo or fetus? A toxic product of alcohol metabolism? One or more of the negative health factors that frequently accompany severe alcoholism? All of these factors?

Experimental animal models of FAS have proven very valuable, especially in answering the basic question: Is alcohol teratogenic? Such studies have demonstrated conclusively that alcohol or one or more of its metabolites is teratogenic; it causes birth defects. Investigations with a variety of species (Randall et al. 1977; Abel 1979; Ellis and Pick 1980; Potter et al. 1980; Dexter et al. 1980; Altshuler and Shippenberg 1981; Clarren and Bowden 1982; Bowden et al. 1983; Clarren and Bowden 1984) have clearly demonstrated the ability to produce birth defects similar to those in children with FAS.

Animal studies have also allowed the relationship between alcohol dose and degree of malformation to be demonstrated (Ellis and Pick 1980; Rasmussen and Christensen 1980; Randall et

al. 1981). For example, in experiments by Ellis and Pick (1980), malformations in newborn dogs varied in nature and severity according to the amount of alcohol administered to mothers during gestation. Higher doses produced spontaneous abortions, increased growth retardation, and early mortality as well as a greater number of malformations. Rasmussen and Christensen (1980) found clear relationships between alcohol dose and number of malformations in similar experiments with mice. Randall and colleagues (Randall et al. 1981) found nearly linear dose-response gradations in a comparison of the teratogenic and growth impairment effects of three doses of alcohol in pregnant mice (figures 8 and 9). Infant mortality and fetal resorptions (the

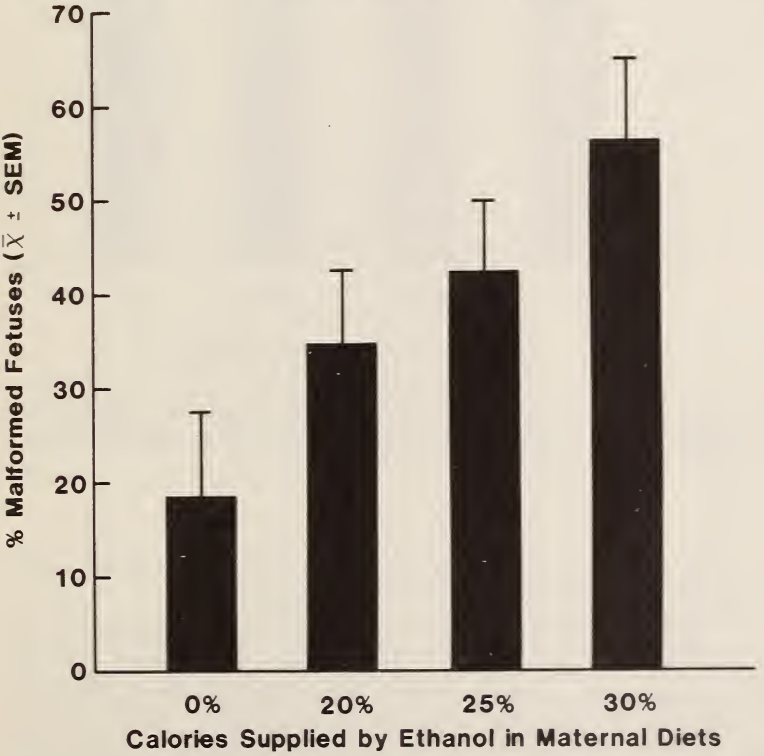

Figure 8.—Relationship between alcohol dose to pregnant mice and rate of malformations in fetuses. Percentage of malformed fetuses increases with increased percentage of maternal calories supplied by alcohol.

SOURCE: Randall et al. 1981.

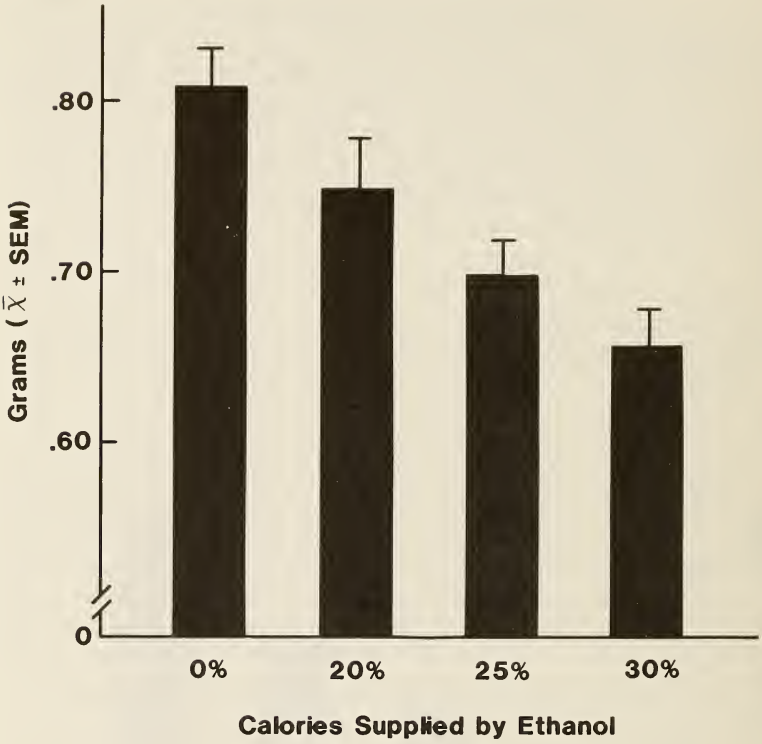

Figure 9.—Inverse relationship between alcohol dose to pregnant mice and fetal weight. Average fetal weight declines with increasing percentage of maternal calories derived from alcohol.
SOURCE: Randall et al. 1981.

equivalent of miscarriage in humans) were highest in the group that received 30 percent of calories as alcohol.

Animal studies also have shown that these effects are not caused by poor nutrition or other factors of the kind that frequently accompany human alcoholism; they are caused either by alcohol itself or by one of its metabolic products. In addition to showing a dose-response relationship, the study by Randall and her colleagues (Randall et al. 1981) demonstrated why alcohol, and not these other factors, must be primarily responsible for the malformations. These investigators controlled the nutrition of their experimental mice to make sure alcoholic animals and con-

trol animals received the same number of calories and other nutrients in their diets. They found that restricting caloric intake in these animals could not produce the teratogenic effects they observed in the offspring of alcoholic mice; it was the alcohol that made the difference, in a dose-dependent manner.

Animal models are also likely to increase our understanding of the interrelatedness of facial malformations, behavioral anomalies, and neuroanatomical and neurochemical abnormalities in the human FAS. There is good reason to think that all of these features may be related to the same toxic event in early embryonic life. Components of both the brain and the face, particularly the midface, arise from the same primordial embryonic structure, and it may be that alcohol causes both the brain damage and the facial malformations by damaging that structure. Consistent with this idea is a peculiarity of FAS that has already been mentioned in this report—that children with the most severe facial malformations of FAS also have the most brain damage, the most severe mental retardation, and the least chance of showing improvement. Further development of animal models will probably yield much-needed information in this important area.

In the earliest days of FAS animal research, the main goal was to verify that alcohol administration during pregnancy could indeed produce birth defects and to show that alcohol itself, not some other associated factors, was the cause of FAS. This goal has been accomplished; we now know from animal studies that alcohol can cause birth defects.

What remains to be learned, however, is *how* alcohol causes birth defects. What specific events occur at the cellular and molecular levels during development that get translated into physical anomalies and behavioral and neurological deficits? Are there periods during pregnancy when the embryo or fetus is especially vulnerable? What are the underlying mechanisms of the fetal alcohol syndrome and other alcohol-related birth defects? As with the demonstration of alcohol teratogenicity, answers to these crucial questions can only be obtained by experiments with laboratory animals.

The following sections describe some recent research aimed at answering these questions. Major emphasis is on studies of prenatal

brain damage because, from a human perspective, it is mental impairment that is the most tragic aspect of FAS. Furthermore, neurological effects from prenatal alcohol exposure may well be observed at drinking levels below those associated with FAS.

Effects of Prenatal Alcohol Exposure on Brain Development

Damage to the developing brain has long been recognized as one of the most serious consequences of heavy alcohol consumption during pregnancy. The extreme vulnerability of the brain to prenatal alcohol damage is suggested by the fact that such damage can occur even in the absence of outward physical abnormalities arising from in utero alcohol exposure, as indicated by epidemiological studies such as those in Seattle and by laboratory studies (Barnes and Walker 1981; West et al. 1981a, 1981b). A number of investigators have therefore been using animal models to examine the effects of prenatal ethanol exposure on specific structures within the brain.

Anatomical Studies of Alcohol-Exposed Embryo Brains

A recent electron microscopic study of mouse embryos exposed to high alcohol doses (Sulik et al. 1984) has revealed gross brain anomalies that are strikingly similar to those seen in human FAS. The results of the study also point to a specific stage of early embryonic development as a possibly critical period of susceptibility to alcohol damage.

Sulik and her colleagues examined the consequences for prenatal brain development of acute alcohol administration to pregnant mice on the seventh day of gestation, a time corresponding embryologically to the third week of human pregnancy. In mice, this is the period of pregnancy when the embryo is entering the gastrula stage, a phase of development in which the embryo takes the form of a "hollow ball" of cells. Gastrulation is an embryonic phase common to all animal species, including humans.

The researchers investigated the gastrulation stage because one of its features is the formation of a structure called the embryonic disc, which later differentiates to give rise to parts of the brain as well as features of the midface. Because brain damage and midfacial malformation are major features of FAS, the

investigators reasoned that the time of formation of the embryonic disc forms could be a critical period for alcohol-induced embryonic damage leading to FAS, including its characteristic facial, cranial, and brain anomalies as well as behavioral deficits and mental retardation. An intoxicating dose of alcohol was administered to mice on the seventh day of pregnancy. A few days later the embryos were examined microscopically.

Scanning electron microscopy, a technique that yields photographic enlargements with almost three-dimensional quality, as well as conventional light microscopy of tissue sections revealed a number of gross abnormalities in the brains and faces of alcohol-exposed embryos. The brain abnormalities included developmental deficiencies in the forebrain; abnormal development of the primordial hippocampus; malformations in the cerebrum, cerebellum, and other brain structures; and overall reduction in brain size. Facial anomalies included reduced size of the nose, abnormally small separation of the nostrils, underdeveloped philtrum, abnormally shallow notch in the upper lip, and an exaggerated space between the nose and the upper lip. Nearly all of these brain and facial anomalies are classic features of human FAS.

The significance of these findings is that they point to a period corresponding embryologically to the third week of human pregnancy as a time when the embryo may be especially vulnerable to teratogenic actions of alcohol that produce major features of FAS (although alcohol can damage the developing infant in various ways throughout gestation). If these findings can be extrapolated to human pregnancy, this alcohol-vulnerable stage of embryonic development would occur at a time when most pregnant women are still unaware of their pregnancy.

Alcohol Damage to the Hippocampus: A Possible Link to Learning Deficits

The hippocampus, a nervous system structure lying near the center of the brain, is receiving considerable attention from researchers as a model system for studying prenatal alcohol effects on central nervous system development. A major reason for studying this structure is evidence that it may be involved in learning, a function that is conspicuously impaired in FAS.

Several studies have shown pronounced effects of prenatal alcohol exposure on the development of the fetal hippocampus,

including dramatic reduction in hippocampal nerve cells (Barnes and Walker 1981) and incorrect termination of hippocampal nerve cells (West et al. 1981a, 1981b; West and Hodges-Savola, 1982). The abnormal "wiring" of the brain persisted in the prenatally exposed rats until 9 months of age (the oldest animals tested), and it occurred even in the absence of any external malformations in the animals. The evidence from these and other studies (West and Hamre 1985) is that alcohol exposure in prenatal life, during periods of brain development roughly equivalent to all three trimesters of human pregnancy, can cause abnormalities in the hippocampus.

The functional significance of some of these alcohol-induced abnormalities in the hippocampus is not known with any certainty, but there is evidence suggesting that they might contribute to learning deficits. A correlation has been demonstrated between displaced hippocampal nerve cell terminations and impaired learning in rodents (Lipp et al. 1984; Schwegler et al. 1981).

Riley and his colleagues have also demonstrated impaired conditioned learning in rats prenatally exposed to alcohol (Riley et al. 1984). Conditioned learning is a process of training animals to avoid something they would otherwise seek. The learning deficits appeared to be related to faulty hippocampal development, a finding consistent with other studies showing that the hippocampus is involved in this type of learning (Driscoll et al. 1982; Gemberling et al. 1980; Gregg et al. 1978).

In summary, these studies indicate that irreversible damage to the hippocampus can be produced by prenatal alcohol exposure, that such damage can occur at stages of development corresponding to all three trimesters of human pregnancy, and that alcohol-caused damage to the hippocampus is associated with measurable deficits in the ability to learn. The implications for human pregnancy could be substantial.

Alcohol Damage to the Developing Cerebral Cortex

A recent study in rats (Miller 1986) found that development of the cerebral cortex, a brain structure that is a major site of mental activity and control of motor functions, can be profoundly affected by prenatal exposure to alcohol. In the offspring of female rats fed alcohol (as 37 percent of total calories) during pregnancy, the effects included delay and prolongation of the period during which

cortical nerve cells are formed, reductions in the final number of these nerve cells, and abnormalities in their distribution. Damage to the developing cortex in human FAS has long been inferred from behavioral observations of the children made in the light of knowledge of this brain structure's known functions in mental processes and motor functions. Abnormalities in FAS children include problems with such cortical functions as cognition, muscle control, and fine motor skills. These findings in rats provide direct physical evidence that alcohol damage to the developing cerebral cortex may be involved in the characteristic cognitive and motor deficiencies of human FAS.

Effects of Alcohol on the Developing Visual and Auditory Systems

A number of visual system anomalies are found in FAS, including strabismus, abnormal width between the eyes (hypertelorism), and small eyes (microophthalmia). Prenatal alcohol exposure has also been shown to cause atrophy of the optic disc (the point where the optic nerve enters the retina), malformed retinal blood vessels, subnormal number of optic nerve axons, and blindness (Stromland 1981; Laale 1971; Papara-Nicholson and Telford 1957).

Recently, Church and Holloway (1984), using a technique called brainstem auditory evoked potential (BAEP) audiometry, demonstrated that prenatal alcohol exposure can also impair development of the sense of hearing in rats. The BAEP is a series of electrical waves that arise in the brainstem in response to high-frequency clicking sounds, and its various components reflect neurological events at several points along the auditory pathway. These investigators found that the delay (latency) between the click stimulus and the generation of the BAEP (a matter of milliseconds) grew progressively shorter with age both in rats prenatally exposed to alcohol and in controls, reflecting postnatal development of the auditory pathway in both groups. However, the progressive shortening of BAEP latency with age was considerably slower in rats whose mothers consumed alcohol during pregnancy, and their BAEP waves were also considerably weaker. Furthermore, the alcohol-exposed rats never overcame their hearing deficiency. Although the differences between the groups

were greatest early in postnatal development, the alcohol-exposed rats still had significantly longer BAEP latency at maturity. Thus prenatal alcohol exposure impaired maturation of the sense of hearing in these animals and probably caused permanent hearing deficits.

Neurobehavioral Effects of Prenatal Alcohol Exposure in Animals

As noted in the discussion of human longitudinal studies, neurobehavioral effects can occur at lower levels of maternal drinking during pregnancy, even in the absence of physical anomalies. Children born to chronic alcoholic women often show mental retardation, hyperactivity, and perceptual-motor dysfunction, and children born to women who drink at lower levels can show more subtle neurobehavioral deficits. A number of studies over the years have shown that rats and other laboratory animals exposed to alcohol prenatally exhibit similar neurobehavioral abnormalities.

Recent reports of research using animal models of neurobehavioral impairment are discussed in this section. Significant new research in this area includes the effects of prenatal alcohol exposure on sucking behavior, learning, and sexual development, as well as the use of animal models to test potential treatments of fetal alcohol behavioral effects. Findings from these studies appear highly relevant to prenatal alcohol exposure in humans.

Sucking Behavior

As shown in the Seattle longitudinal study, human infants exposed to alcohol prenatally have been found to have weak sucking responses and to take longer to begin sucking when presented with an appropriate stimulus (Martin et al. 1979; Stock et al. 1985). These effects have recently been replicated in rats (Chen et al. 1982).

The sucking response is one of the first responses displayed by infant rats, and its development follows a well-defined pattern. Until about 12 days of age, rat pups quickly attach to a nipple, whether they are hungry or not. After the 12th day of life, however, hungry pups continue to attach rapidly but nondeprived pups attach progressively more slowly.

Because this pattern is so well-defined, Chen and colleagues reasoned that nipple attachment behavior in young rats might be ideal for detecting a developmental dysfunction resulting from prenatal alcohol exposure. Their studies revealed that prenatal exposure to alcohol significantly slowed the speed of attachment in animals 3 to 9 days of age. These effects of prenatal alcohol exposure occurred regardless of maternal diet, whether the pups were tested singly or in groups, and whether they were raised by their alcohol-fed biological mothers or by surrogates. Thus impaired sucking in the young rats was evidently caused by their prenatal alcohol exposure, and not by maternal variables in postnatal life. These animal experiments complement the clinical observations of Martin and colleagues (Martin et al. 1979; Stock et al. 1985) of impaired sucking in human infants born to mothers who consumed alcohol in "social" amounts during pregnancy. Sucking is vital to infant nutrition, and its impairment may play a role in retarded postnatal growth, one of the primary consequences of prenatal alcohol exposure (Streissguth, Landesman-Dwyer et al. 1980).

Effects on Sexual Development

Because chronic alcohol exposure in adult men and women is known to cause disturbances in reproductive function (Cicero et al. 1979; Cicero 1981; Van Thiel et al. 1975, 1977, 1978), particularly in the levels of sex hormones, it is conceivable that it might cause similar disturbances in utero, especially since alcohol passes readily through the placenta and into the fetus.

Several animal studies have suggested that prenatal alcohol exposure does indeed produce effects on the developing endocrine system and furthermore that these effects may persist into adult life. There have been reports of altered levels of gonadal hormones and corticosterone (Kakihana et al. 1980; Rose et al. 1981) and altered sexual development (Boggan et al. 1979; Chen and Smith 1979) in the offspring of animals fed alcohol during gestation.

Recently, McGivern and colleagues (1984) reported that prenatal alcohol exposure altered preference for saccharin in male and female rats. Female rats normally have a stronger preference for saccharin solutions than males, a behavior that is said to be

"sexually dimorphic." Prenatal alcohol exposure altered this behavior in male and female rats, making the males more female-like and the females more male-like in their preference for saccharin. These investigators speculate that the "feminized" behavior in the males may be caused by decreased testosterone levels during fetal life and that the "masculinized" behavior in the females may be caused by increased secretion of adrenal steroid hormones. These findings support a hypothesis that endocrine imbalance from prenatal alcohol exposure can have long-term consequences (Anderson 1981).

A hypothesis of endocrine imbalance is also suggested by a recent report by Barron and Riley (1985) that prenatal exposure to alcohol significantly reduces nurturing behavior in adult and juvenile rats of either sex. After about a week of exposure to rat pups, both males and females will groom them, retrieve them if they stray from the nest, and hover over them in a nursing posture. The behavior is not under hormonal control in the adults, but previous studies have revealed that its initial appearance is significantly influenced by hormonal factors during prenatal life (Rosenblatt et al. 1979). This suggests that alcohol's known ability to disturb the developing endocrine system in utero might cause interference with the subsequent development of nurturing behavior.

In studies to test this hypothesis, adult females exposed to alcohol prenatally showed significant deficits in nurturing behavior. They were about half as fast as controls in retrieving strayed pups, spent about half as much time hovering near or over them as the control rats, and had a greater tendency to cannibalize the young (a behavior more typical of adult male rats). When the tests were performed with juvenile rats, both sexes showed impairment of spontaneous nurturing behavior. Significantly, the impairment dissipated with age in the males but not in the females.

THE MECHANISMS OF FETAL ALCOHOL DAMAGE

The actual mechanisms of alcohol-induced birth defects are still unknown, although numerous studies show that alcohol and acetaldehyde, its first metabolite, are directly toxic to the embryo and that alcohol can interfere with systems involved in the maintenance of pregnancy. It is likely that several mechanisms are involved, and that different mechanisms may underlie alcohol-induced retardation of fetal growth and alcohol-induced congenital anomalies.

Almost all of what is known about the possible mechanisms involved in the production of birth defects by alcohol has been derived from experiments with animals. The main effects of alcohol are in two broad areas: (1) direct damage to the embryo by alcohol or by acetaldehyde, and (2) alcohol's indirect effects on maternal mechanisms involved in the maintenance of pregnancy.

Among the possibilities being examined, in addition to direct toxic effects of alcohol and its metabolites on the embryo and fetus, are impaired transport of nutrients from the mother to the fetus, impaired delivery of oxygen to the fetus, derangements of DNA and RNA metabolism, and impaired protein synthesis (see review by Abel 1983). One of the newest areas in the search for mechanisms of alcohol teratogenicity is the prostaglandin system. Selected examples of research in these areas are presented in the following sections.

Direct Toxicity of Alcohol on Embryos

Most substances that circulate in the blood of a pregnant woman can pass through the placenta and enter the fetus, either by simple diffusion or by active biochemical transport mechanisms. This property of the placenta is the basis of its normal functions in pregnancy, which are to supply oxygen and nutrients to the fetus and to remove the waste products of fetal metabolism. Unfortunately, the placenta provides no barrier to the passage of many substances that can harm the fetus, including alcohol, which diffuses very readily through the placental membranes and into the fetal circulation.

It has been known for many years that alcohol in the fetal blood reaches about the same concentration as in the maternal blood, and experiments have shown that alcohol itself is directly

toxic to embryos. For example, in one study alcohol solutions were applied to embryos that were removed from pregnant rats and grown in tissue culture medium (Brown et al. 1979), a method that eliminates confounding maternal factors. Alcohol solutions applied to these embryos around the 10th day of development caused a reduction both in overall embryonic growth and in the normal differentiation of embryonic tissues into new structures. The disruption of normal development, which varied in degree according to the dose of alcohol, was found to be due to a reduction in the number of embryonic cells.

Nutritional Deficiencies in the Mother

Alcohol abuse is often accompanied by vitamin deficiencies, including thiamine, folate, and pyridoxine deficiency, as well as deficiencies in trace minerals such as zinc. Such deficiencies, when severe, have on their own been associated with birth defects in offspring (Hurley 1979). It is therefore conceivable that they might play a contributory role in FAS and related disorders.

Selective Fetal Malnutrition

Animal experiments have provided evidence that alcohol can interfere with the transport of amino acids, the constituents of proteins, from the maternal circulation through the placenta to the fetus. This raises the possibility that the fetus could become deficient in certain essential amino acids even if the mother is adequately nourished (Fisher et al. 1981; Henderson et al. 1981; Lin 1981). Alcohol has also been shown to inhibit the synthesis of protein in the brain, heart, and other fetal organs (Israel et al. 1968; Rawat 1975, 1976, 1979). The consequences of such effects could include diminished fetal growth, higher fetal mortality, low birthweight, and congenital defects.

The Possible Role of Prostaglandins in Fetal Alcohol Damage

An intriguing and potentially very important hypothesis arising from recent research is that prostaglandins may be involved in some way in the mechanism of alcohol-induced birth defects. Prostaglandins are a family of complex derivatives of polyunsaturated fatty acids whose normal function is to modulate certain cellular functions in the body. These compounds are

biologically potent and have a hormone-like action in that they can be produced in one part of the body and cause effects at distant sites. Excess production of certain prostaglandins is involved in pain and inflammation, for example, and it is significant that one of the most effective drugs for treating those conditions—aspirin—is an inhibitor of prostaglandin synthetase, a key enzyme in the synthesis of prostaglandins (Vane 1978).

It has been proposed that prostaglandins may play a role in the etiology of alcohol-induced birth defects (Pennington et al. 1983), and there is evidence from animal studies that aspirin and other prostaglandin synthetase inhibitors can antagonize some prostaglandin-mediated effects of alcohol. These include alcohol-induced sleep (George and Collins 1979), hypothermia (lowered body temperature) (George et al. 1983), and increased activity (Ritz et al. 1981) in adult mice.

In view of these previous reports, Randall and Anton (1984) tested whether aspirin might antagonize the teratogenic actions of alcohol. Animals received alcohol, aspirin, or appropriate control substances in a study involving only a single-dose exposure. A striking finding was that there were less than half as many malformations in the fetuses of mice that had received aspirin before alcohol compared to control animals: 25 percent versus 54 percent (table 1), though the alcohol-aspirin group still had three to five times as many malformations as the control groups. Also, aspirin pretreatment markedly reduced alcohol-induced fetal mortality (table 2).

It is important to emphasize that these findings do not mean a pregnant woman may now drink safely as long as she takes

Table 1.—Effect on Number and Type of Malformation

Group	No. live fetuses abnormal/total	No. litters with abnormal fetuses/total treated	No. with abnormality			
			Limb	Kidney	Heart	Eye
BS	5/64 (8%)	4/8	1	2	0	2
AS	3/64 (5%)	3/9	0	3	0	0
BA	38/71 (54%)	10/11	24	26	3	5
AA	19/75 (25%)	8/9	10	13	3	2

SOURCE: Randall and Anton 1984.

Table 2.—Effect on Live Births, Prenatal Mortality, and Fetal Weight

Group	No. mothers treated	Mean no. live fetuses/litter	Total no. resorbed/dead fetuses	Mean live fetal weight (g ± SE)
BS	8	8.0 ± 0.53	2	1.09 ± 0.06
AS	9	7.3 ± 0.31	5	1.03 ± 0.02
BA	11	6.5 ± 0.89	23	0.91 ± 0.09
AA	9	8.3 ± 0.33	3	0.96 ± 0.07

BS = Control animals receiving buffer and saline
AS = Control animals receiving aspirin and saline
BA = Test animals receiving buffer and alcohol
AA = Test animals receiving aspirin and alcohol

SOURCE: Randall and Anton 1984.

aspirin beforehand. These studies were done on a different species, the dose of aspirin was high, and it was injected. Furthermore, aspirin is not a risk-free drug even in normal doses; several studies have shown that the combination of aspirin and alcohol carries an increased risk of gastric bleeding. Research also shows that aspirin in early pregnancy is associated with a twofold increase in risk of a specific congenital heart defect (Zierler and Rothman 1985). Finally, aspirin did not prevent birth defects in these animals; it only reduced their frequency to a level that was still very high.

The real significance of this study is that it opens up potentially fruitful new areas of research to understand the mechanisms behind alcohol-caused birth defects. Although there is good reason to suspect the involvement of prostaglandins in alcohol teratogenesis, further work is needed to demonstrate conclusively that aspirin prevents alcohol-related birth defects by interfering with prostaglandins. The investigators point out that other possible actions of aspirin besides inhibition of prostaglandin synthesis, such as alterations in alcohol metabolism, might also explain their results.

ALCOHOL AND FETAL DAMAGE: A SUMMATION

The picture that is emerging from numerous animal studies such as those cited above, as well as from human epidemiology studies, is that alcohol consumption during pregnancy can produce effects on offspring ranging from extremely subtle to severe, probably depending on alcohol dose, timing, and consumption pattern. More research is needed to fill numerous gaps in the picture, but its general outlines are evident:

Very early in pregnancy, alcohol or a metabolic product may either kill embryos outright or may cause damage that leads to death in the womb later. This might explain the high rate of miscarriages and stillbirths associated with maternal alcoholism, which was reported as far back as 1899 by Sullivan and has now been confirmed by modern studies. Harlap and Shiono (1980), for example, found a statistically significant increase in spontaneous abortions during the second trimester among women who reported alcohol intakes as low as 15 to 30 grams a day (roughly equivalent to one to two standard drinks[2]). Damage by this mechanism could occur before a woman even knew she was pregnant.

Alcohol or a metabolic product may cause excessive cell death in the developing central nervous system and may interfere with cell migration, a process essential for the proper development and organization of the brain, skull, and face. As shown in the animal studies described in the preceding section, the results may range from brain tissue disorganization that is detectable only under a microscope (for example, abnormal termination of nerve fibers in the hippocampus) to gross malformation of some brain structures (as in the electron microscope studies of rodent embryos). Autopsies on deceased babies whose alcoholic mothers exposed them to alcohol in utero have also revealed this range of brain anomalies (Clarren et al. 1979; Pfeiffer et al. 1979). Furthermore, since parts of the brain, skull, and face all differentiate from the same embryonic tissue around the gastrulation phase of pregnancy, cell death or impaired cell migration caused

[2] A standard drink is 12 ounces of beer, 5 ounces of wine, or 1 1/2 ounces of 80-proof distilled spirits (whether served straight or diluted with a mixer such as ginger ale or club soda). In these quantities, all three beverages have about the same alcohol content, i.e., slightly more than half an ounce of absolute (pure) alcohol.

at that time by alcohol or a metabolic product could account for three major features of FAS: severe mental deficiency, small head size, and facial malformations (Frias et al. 1982). Again, damage by this mechanism could occur before a woman knew she was pregnant.

Alcohol may continue to interfere with cell migration and development in later pregnancy. Repair mechanisms begin to operate in the later stages, however, and they may allow development of the central nervous system to be completed, as has been shown in recent experiments with rats (Volk et al. 1981). The repair may not be complete; studies also have shown that if nerve cells in the developing brain are not in the right place at the right time they cannot form normal connections (synapses) with each other for the transmission of nerve impulses (Volk et al. 1981; Shimada et al. 1982).

Alcohol consumption by pregnant rats has been found to interfere with fetal endocrine mechanisms responsible for growth (Thanadi and Schanberg 1979). If this is also true of humans, an alcohol-induced shortage of these hormones in the fetus could account for some of the growth deficiency seen in the children of women who drink during pregnancy. Growth deficiency is one of the most consistently reported features of such children, even when their mothers drank at moderate levels.

IS ANY AMOUNT OF DRINKING SAFE DURING PREGNANCY?

The consensus of most experts in the field is that effects of alcohol on the developing organism lie on a dose-dependent continuum ranging from severe and frequent anomalies in the offspring of pregnant alcoholic women to subtle and infrequent neurobehavioral effects at lower consumption levels. After the Department of the Treasury and the Department of Health and Human Services published a report on health hazards associated with alcohol (Department of the Treasury/DHHS 1980), which reviewed findings on FAS and FAE, the Surgeon General of the United States issued a health advisory recommending that women not drink alcoholic beverages during pregnancy. He urged that health professionals inquire routinely about alcohol consumption by patients who are pregnant or considering pregnancy, and noted that women who drink alcohol "at amounts consistent with the diagnosis of alcoholism" risk bearing children with FAS (Surgeon General 1981).

This recommendation was based on two considerations: first, knowledge of the clear risks posed by heavy alcohol use in pregnancy and, second, the reasonable supposition that risk, albeit lower risk, could therefore be associated with lower levels of drinking. Many medical and public health experts consider this a prudent recommendation that should be followed until research has demonstrated a safe level of alcohol use in pregnancy. So far evidence does not exist to establish a safe level of alcohol consumption by pregnant women.

EDUCATION PROGRAMS

Several programs have been instituted by Federal, State, and private agencies since the late 1970s to alert and educate the public about FAS and the risks of drinking during pregnancy. These include components of prevention campaigns sponsored by the National Institute on Alcohol Abuse and Alcoholism and the U.S. Treasury Department, as well as programs sponsored by State agencies and private foundations. Major emphasis has been placed on media advertising campaigns and community outreach programs.

Overall, these programs have been successful in making many people aware of the risks associated with drinking during pregnancy. A survey by the Opinion Research Corporation (1979), for example, found that nearly 70 percent of respondents in the Western States had heard or read about the effects of alcohol on the fetus.

In a survey by researchers from the University of Washington (Little et al. 1981), 90 percent of respondents sampled in Multnomah County, Oregon (Portland and vicinity), spontaneously mentioned consumption of at least one alcoholic beverage by a pregnant woman as possibly harmful to the unborn child. This figure is close to the 92 percent awareness the same investigators found in an earlier survey in King County, Washington (Seattle and vicinity), and to the 96 percent awareness found in Los Angeles County, California, by other investigators (Minor and Van Dort 1980).

Widespread awareness of the risk appears to have decreased the number of women who drink at any level during pregnancy. For example, Streissguth and her colleagues (1983) compared the smoking and drinking habits of women who were pregnant before the widespread publicity about FAS with those of pregnant women 6 years later. They found that more women had become abstainers and that moderate or occasional drinkers were drinking less. Although the overall prevalence of drinking at any level has declined among pregnant women, the percentages of light, moderate, and heavy drinkers among pregnant women have remained about the same among those who do not abstain.

CONCLUSION

Major advances are being made in understanding the effects of prenatal alcohol exposure on the developing organism. Specific brain structures that are especially sensitive to alcohol and are involved in functions known to be impaired in the fetal alcohol syndrome are being identified. Factors that modify the risk that an alcoholic woman will give birth to a baby with FAS are being discovered. Subpopulations that appear to be especially vulnerable to alcohol-related birth defects are beginning to be identified; this area of inquiry can lead to better targeting of prevention efforts. Stages of pregnancy at which the embryo or fetus is especially vulnerable to alcohol are being identified, and promising new leads to understand the underlying mechanisms of FAE and FAS are being explored. Knowledge of the more subtle effects of maternal social drinking on the developing infant is also growing. Finally, because of increasing awareness of the risks, more women are abstaining from alcohol during pregnancy, and light-to-moderate drinkers have reduced their consumption.

These are very encouraging developments. Clearly, the study of FAS and FAE has progressed tremendously since the late 1960s and early 1970s, when the literature on this subject consisted mostly of case reports describing tragically malformed and mentally retarded babies born to alcoholic women. Much more remains to be learned, however.

One of the greatest needs is better understanding of factors that modify the risk of children being born with alcohol-related birth defects. For example, what accounts for black race being a risk factor for FAS? Why do some American Indian populations have an extremely high incidence of FAS? Are genetic factors involved? If genetics plays a role in susceptibility to FAS, can biochemical or other markers of this susceptibility be found so women at risk can be identified during prenatal care and given special counseling? What other factors besides race and beverage type may modify the risk of alcohol-related birth defects? Further research could identify many more contributing risk factors that might be subject to intervention and modification.

Another great need is to learn more about the effects of lower levels of drinking on pregnancy outcome. As discussed in

this report, some prospective studies have found subtle neurobehavioral effects in the offspring of women who consumed alcohol at low or moderate levels during pregnancy. What is the significance of these effects? Will they have lasting effects on school performance and development of life skills? These questions can be answered only by continued prospective studies.

A related issue that needs much more study is the effect of alcohol dose and timing on teratological risk. Again, continued prospective studies can help provide answers, but crucial knowledge must also come from the development of suitable models in which the effects of alcohol dosage and timing can be studied under controlled laboratory conditions and then extrapolated to humans. Such knowledge is critical to our understanding of the extent and nature of risk associated with light and moderate drinking during pregnancy.

Finally, much more information is needed about the mechanisms by which alcohol produces birth defects. This is a very complex area, and probably no single mechanism can account for all the effects of alcohol on the developing organism. A major aspect of this issue involves the potential for reversibility of injury. What is the potential reversibility of a specific alcohol-related injury occurring at a specific time during gestation? Are there pharmacological or other factors that may help bring about such a reversal? What factors apart from continued alcohol use might prevent the reversal of injury?

Although advances in biomedical science may someday make it possible for us to reverse alcohol-derived fetal injury, our more immediate goals are to define those factors that place some individuals at greater risk, to define the nature of risks from moderate drinking, and to develop better prevention approaches, especially approaches that will affect the drinking behavior of women who are most at risk of giving birth to an infant with the fetal alcohol syndrome or an alcohol-related birth defect.

References

Abel, E.L. Prenatal effects of alcohol on adult learning in rats. *Pharmacology, Biochemistry, and Behavior* 10:239-243, 1979.

Abel, E.L. *Marijuana, Tobacco, Alcohol, and Reproduction*, Chap. 15, Fetal alcohol syndrome. Boca Raton, FL: CRC Press, 1983.

Altshuler, H.L., and Shippenberg, T.S. A subhuman primate model for fetal alcohol syndrome research. *Neurobehavioral Toxicology and Teratology* 3:121-126, 1981.

Anderson, R.A. Endocrine balance as a factor in the etiology of the fetal alcohol syndrome. *Neurobehavioral Toxicology and Teratology* 3:89-104, 1981.

Barnes, D.E., and Walker, D.W. Prenatal ethanol exposure permanently reduces the number of pyramidal neurons in rat hippocampus. *Developmental Brain Research* 1:333-340, 1981.

Barron, S., and Riley, E.P. Pup-induced maternal behavior in adult and juvenile rats exposed to alcohol prenatally. *Alcoholism: Clinical and Experimental Research* 9:360-365, 1985.

Boggan, W.O.; Randall, C.L.; and Dodds, H.M. Delayed sexual maturation in female C57/6J mice prenatally exposed to alcohol. *Research Communications in Chemical Pathology and Pharmacology* 23:117-125, 1979.

Bowden, D.M.; Weathersbee, P.S.; Clarren, S.K.; Fahrenbruch, C.E.; Goodlin, B.L.; and Caffery, S.A. A periodic dosing model of fetal alcohol syndrome in the pigtailed macaque (*Macaca nemestrina*). *American Journal of Primatology* 4:143-157, 1983.

Brown, N.A.; Goulding, E.H.; and Fabro, S. Ethanol embryotoxicity: Direct effects on mammalian embryos in vitro. *Science* 206:573-575, 1979.

Chen, J.J., and Smith, E.R. Effects of prenatal alcohol on sexual differentiation and open-field behavior in rats. *Hormones and Behavior* 13:219-231, 1979.

Chen, J.-S.; Driscoll, C.D.; and Riley, E.P. Ontogeny of suckling behavior in rats prenatally exposed to alcohol. *Teratology* 26:145-153, 1982.

Church, M.W., and Holloway, J.A. Effects of prenatal ethanol exposure on the postnatal development of the brainstem auditory evoked potential in the rat. *Alcoholism: Clinical and Experimental Research* 8:258-265, 1984.

Cicero, T.J. Neuroendocrinological effects of alcohol. *Annual Review of Medicine* 32:123-142, 1981.

Cicero, T.J.; Meyer, E.R.; and Bell, R.D. Effects of ethanol on the hypothalamic-pituitary-luteinizing hormone axis and testicular steroidogenesis. *Journal of Pharmacology and Experimental Therapeutics* 208:210-215, 1979.

Clarren, S.K. Recognition of fetal alcohol syndrome. *Journal of the American Medical Association* 245:2436-2439, 1981.

Clarren, S.K. The diagnosis and treatment of fetal alcohol syndrome. *Comprehensive Therapy* 8:41-46, 1982.

Clarren, S.K., and Bowden, D.M. The fetal alcohol syndrome: A new primate model for binge drinking and its relevance to human ethanol teratogenesis. *Journal of Pediatrics* 101:819-824, 1982.

Clarren, S.K., and Bowden, D.M. Measures of alcohol damage in utero in the pigtailed macaque (*Macaca nemestrina*). In: *Mechanisms of Alcohol Damage in Utero*. CIBA Foundation Symposium No. 105. London: Pitman Publishing Ltd., 1984, pp. 157-172.

Clarren, S.K., and Smith, D.W. The fetal alcohol syndrome. *New England Journal of Medicine* 298:1063-1067, 1978.

Clarren, S.K.; Alvord, E.C.; Sumi, S.M.; Streissguth, A.P.; and Smith, D.W. Brain malformations related to prenatal exposure to ethanol. *Journal of Pediatrics* 92:64-67, 1979.

Dehaene, P.; Crepin, G.; Delahousse, G.; Querleu, D.; Walbaum, R.; Titran, M.; and Samaille-Villette, C. Aspects epidemiologiques du syndrome d'alcoolisme foetal (Epidemiological aspects of the fetal alcohol syndrome). *La Nouvelle Presse Medicale* 10:2639-2643, 1981.

Dehaene, P.; Semaille-Villette, C.; Samaille, P.; Crepin, G.; Walbaum, R.; Deroubaix, P.; and Blanc-Garin, A.P. Le syndrome d'alcoolisme foetal dans le nord de la France (The fetal alcohol syndrome in the north of France). *Revue de l'Alcoolisme* (Paris) 23:145-158, 1977.

Dewey, S.L., and West, J.R. Organization of the commissural projection to the dentate gyrus is unaltered by heavy ethanol exposure during gestation. *Alcohol* 2:617-622, 1985.

Dexter, J.D.; Tumbleson, M.E.; Decker, J.D.; and Middleton, C.C. Fetal alcohol syndrome in Sinclair (S-1) miniature swine. *Alcoholism: Clinical and Experimental Research* 4:146-151, 1980.

Driscoll, C.D.; Chen, J.-S.; and Riley, E.P. Passive avoidance performance in rats prenatally exposed to alcohol during various periods of gestation. *Neurobehavioral Toxicology and Teratology* 4:99-103, 1982.

Ellis, F.W., and Pick, J.R. An animal model of the fetal alcohol syndrome in beagles. *Alcoholism: Clinical and Experimental Research* 4:123-134, 1980.

Ernhart, C.B.; Wolf, A.W.; Linn, P.L.; Sokol, R.J.; Kennard, M.J.; and Filipovich, H.F. Alcohol-related birth defects: Syndromal anomalies, intrauterine growth retardation, and neonatal behavioral assessment. *Alcoholism: Clinical and Experimental Research* 9:447-453, 1985.

Fisher, S.E.; Atkinson, M.; Van Thiel, D.H.; Rosenblum, E.; David, R.; and Holzman, I. Selective fetal malnutrition: The effect of ethanol and acetaldehyde upon in vitro uptake of alpha amino isobutyric acid by human placenta. *Life Sciences* 20:1283-1288, 1981.

Frias, J.L.; King, G.J.; and Williams, C.A. Cephalometric assessment of selected malformation syndromes. *Birth Defects* 18:139-150, 1982.

Galton, F. *Natural Inheritance*. London: MacMillan, 1899.

Gemberling, G.A.; Domjan, M.; and Amsel, A. Aversion learning in 5-day-old rats: Taste-toxicosis and texture-shock associations. *Journal of Comparative Physiological Psychology* 94:734-735, 1980.

George, F.R., and Collins, A.C. Prostaglandin synthetase inhibitors antagonize the depressant effects of ethanol. *Pharmacology, Biochemistry, and Behavior* 10:865-869, 1979.

George, F.R.; Howerton, T.C.; Elmer, G.I.; and Collins, A.C. Antagonism of alcohol hypnosis by blockade of prostaglandin synthesis and activity: Genotype and time course effects. *Pharmacology, Biochemistry, and Behavior* 19:131-136, 1983.

Gregg, B.; Kittrell, E.M.W.; Domjan, M.; and Amsel, A. Ingestional aversion learning in preweanling rats. *Journal of Comparative Physiological Psychology* 92:785-795, 1978.

Gusella, J.L., and Fried, P.A. Effects of maternal social drinking and smoking on offspring at 13 months. *Neurobehavioral Toxicology and Teratology* 6:13-17, 1984.

Haggard, H.W., and Jellinek, E. *Alcohol Explored*. New York: Doubleday and Co., 1942.

Hanson, J.W.; Streissguth, A.P.; and Smith, D.W. The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. *Journal of Pediatrics* 92:457-460, 1978.

Harlap, S., and Shiono, P.H. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 2:173-176, 1980.

Henderson, G.I.; Turner, D.; Patwhardan, R.V.; Lumeng, L.; Hoyumpa, A.M., Jr.; and Schenker, S. Inhibition of placental valine uptake after acute and chronic maternal ethanol consumption. *Journal of Pharmacology and Experimental Therapeutics* 216:465-472, 1981.

Hurley, L. The fetal alcohol syndrome: Possible implications of nutrient deficiencies. NIAAA Research Monograph 2, Alcohol and Nutrition. Washington, DC: U.S. Government Printing Office, 1979.

Iosub, S.; Fuchs, M.; Bingol, N.; Rich, H.; Stone, R.K.; Gromisch, D.S.; and Wasserman, E. Familial fetal alcohol syndrome: Incidence in blacks and Hispanics. *Alcoholism: Clinical and Experimental Research* 9:185, 1985.

Israel, Y.; Salazar, I.; and Rosemann, E. Inhibitory effects of alcohol on intestinal amino acid transport in vivo and in vitro. *Journal of Nutrition* 96:499-504, 1968.

Jones, K.L., and Smith, D.W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2:999-1001, 1973.

Jones, K.L.; Smith, D.W.; Streissguth, A.P.; and Myrianthopoulos, N.C. Outcome in offspring of chronic alcoholic women. *Lancet* 1:1076-1078, 1974.

Jones, K.L.; Smith, D.W.; Ulleland, C.N.; and Streissguth, A.P. Pattern of malformation in offspring of alcoholic mothers. *Lancet* 1:1267-1271, 1973.

Kakihana, R.; Butte, J.C.; and Moore, J.A. Endocrine effects of maternal alcoholization: Plasma and brain testosterone, dihydrotestosterone, estradiol, and corticosterone. *Alcoholism: Clinical and Experimental Research* 4:57-61, 1980.

Kuzma, J., and Sokol, R.J. Maternal drinking behavior and decreased intrauterine growth. *Alcohol: Clinical and Experimental Research* 6:396-402, 1982.

Laale, H.W. Ethanol induced notochord and spinal cord duplications in the embryo of the zebrafish, Brachydonio rerio. *Journal of Experimental Zoology* 177:51-64, 1971.

LaDrague, P. Alcoholisme et enfants. These pour le doctorat en Medicine, G. Steinheil, ed., Paris, 1901.

Landesman-Dwyer, S.; Keller, L.S.; and Streissguth, A.P. Naturalistic observations of newborns: Effects of maternal alcohol intake. *Alcoholism: Clinical and Experimental Research* 2:171-177, 1978.

Lemoine, P.; Harouseau, H.; Borteryu, J.P.; and Menuet, J.-C. Les enfants de parents alcooliques: Anomalies observees, a propos de 127 cas. *Ouest Medical* 21:476-482, 1968.

Lewis, M. The measurement of individual differences in the young child's central nervous system functioning: The study of attending. In: *Perceptual and Learning Disabilities*, Cruickshank, W.M., and Hallahan, D.P., eds. New York: Syracuse University Press, 1975.

Lin, G.W.-J. Fetal malnutrition: A possible cause of the fetal alcohol syndrome. *Progress in Biochemical Pharmacology* 18:115-181, 1981.

Lipp, H.-P.; Schwegler, H.; and Driscoll, P. Postnatal modification of hippocampal circuitry alters avoidance learning in adult rats. *Science* 225:80-82, 1984.

Little, R.E., and Streissguth, A.P. Alcohol, pregnancy, and the fetal alcohol syndrome. Unit in Alcohol Use and its Medical Consequences: A Comprehensive Teaching Program for Biomedical Education. Project Cork, Dartmouth Medical School, 1982.

Little, R.E.; Grathwohl, H.L.; Streissguth, A.P.; and McIntyre, C. Public awareness and knowledge about the risks of drinking during pregnancy in Multnomah County, Oregon. *American Journal of Public Health* 71:312-314, 1981.

Majewski, F. Alcohol embryopathy: Some facts and speculations about pathogenesis. *Neurobehavioral Toxicology and Teratology* 3:129-144, 1981.

Martin, D.C.; Martin, J.C.; Streissguth, A.P.; and Lund, C.A. Sucking frequency and amplitude in newborns as a function of maternal drinking and smoking. In: *Biomedical Issues and Clinical Effects of Alcoholism*, Galanter, M., ed. New York: Grune and Stratton, 1979.

Mason, S.T. Noradrenalin in the brain: Progress in theories of behavioral function. *Progress in Neurobiology* 16:263-303, 1981.

May, P.A.; Hymbaugh, K.J.; Aase, J.M.; and Samet, J.M. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Social Biology* 30:347-387, 1983.

McGivern, R.F.; Clancy, A.N.; Hill, M.A.; and Noble, E.P. Prenatal alcohol exposure alters adult expression of sexually dimorphic behavior in the rat. *Science* 224:896-898, 1984.

Miller, M.W. Effects of alcohol on the generation and migration of cerebral cortical neurons. *Science* 223:1308-1311, 1986.

Minor, M.J., and Van Dort, B. "Prevention research on the teratogenic effects of alcohol: Findings from a survey in Los Angeles County of women who recently gave birth." Paper presented at the 109th Annual Meeting of the American Public Health Association, Detroit, MI, October 1980.

Olegard, R.; Sabel, K.-G.; Aronsson, M.; Sandin, B.; Johansson, P.R.; Carlson, C.; Kyllerman, M.; Iverson, K.; and Hrbek, A. Effects on the child of alcohol abuse during pregnancy: Retrospective and prospective studies. *Acta Paediatrica Scandinavica* Supplement 275:112-121, 1979.

Opinion Research Corporation. *Public Perceptions of Alcohol Consumption and Pregnancy: A Nationwide Survey Conducted for the Bureau of Alcohol, Tobacco, and Firearms*. ORC Study No. 33710. Princeton, NJ: Opinion Research Corp., 1979.

Ouelette, E.M.; Rosett, H.L.; and Rosman, N.P. Adverse effects on offspring of maternal alcohol abuse during pregnancy. *New England Journal of Medicine* 297:528-530, 1977.

Papara-Nicholson, D., and Telford, I.R. Effects of alcohol on reproduction and fetal development in the guinea pig (abstract). *Anatomical Record* 127:438-439, 1957.

Parker, S.; Mahendra, U.; Gavaler, J.S.; and Van Thiel, D.H. Adverse effects of ethanol upon the adult sexual behavior of male rats exposed in utero. *Neurobehavioral Toxicology and Teratology* 6:289-293, 1984.

Pennington, S.N.; Boyd, J.W.; Kalmus, G.W.; and Wilson, R.W. The molecular mechanism of fetal alcohol syndrome (FAS). I. Ethanol-induced growth suppression. *Neurobehaviorial Toxicology and Teratology* 5:259-262, 1983.

Pfeiffer, J.; Majewski, F.; Fischbach, H.; Bierich, J.R.; and Volk, B. Alcohol embryo- and fetopathy. *Journal of the Neurological Sciences* 41:125-137, 1979.

Potter, B.J.; Belling, G.B.; Mano, M.T.; and Hetzel, B.S. Experimental production of growth retardation in the sheep fetus after exposure to alcohol. *Medical Journal of Australia* 2:191-193, 1980.

Pratt, O.E. What do we know of the mechanisms of alcohol damage in utero? In: *Mechanisms of Alcohol Damage in Utero* (Introduction), CIBA Foundation Symposium 105. London: Pitman Publishing Ltd., 1984, p. 3.

Randall, C.L., and Anton, R.F. Aspirin reduces alcohol-induced prenatal mortality and malformations in mice. *Alcoholism: Clinical and Experimental Research* 8:513-515, 1984.

Randall, C.L.; Burling, T.A.; Lochry, E.A.; and Sutker, P.B. Dose-response effect of prenatal alcohol exposure on fetal growth and development in mice. *Substance and Alcohol Actions/Misuse* 2:349-357, 1981.

Randall, C.L.; Taylor, W.J.; and Walker, D.W. Ethanol-induced malformations in mice. *Alcoholism: Clinical and Experimental Research* 1:219-224, 1977.

Rasmussen, B.B., and Christensen, N. Teratogenic effect of maternal alcohol consumption on the mouse fetus: A histopathological study. *Acta Pathologica Microbiologica Scandinavica* (Section A, Pathology) 80:285-289, 1980.

Rawat, A.K. Ribosomal protein synthesis in the fetal and neonatal rat brain as influenced by maternal ethanol consumption. *Research Communications in Chemical and Pathological Pharmacology* 12:723-732, 1975.

Rawat, A.K. Effect of maternal ethanol consumption on foetal and neonatal rat hepatic protein synthesis. *Biochemical Journal* 160:653-661, 1976.

Rawat, A.K. Derangement in cardiac protein metabolism in fetal alcohol syndrome. *Research Communications in Chemical and Pathological Pharmacology* 25:365-375, 1979.

Riley, E.P.; Barron, S.; Driscoll, C.D.; and Chen, J.-S. Taste aversion learning in preweanling rats exposed to alcohol prenatally. *Teratology* 29:325-331, 1984.

Ritz, M.C.; George, F.R.; and Collins, A.C. Indomethacin antagonizes ethanol-induced but not pentobarbital-induced behavioral activation. *Substance and Alcohol Actions/Misuse* 2:289-299, 1981.

Rouquette, J. Influence de l'intoxication alcoolique parentele sur le developpement physique et psychique des jeunes enfants. Thesis, Paris, 1957.

Rose, J.C.; Meis, P.J.; and Castro, M.I. Alcohol and fetal endocrine function. *Neurobehavioral Toxicology and Teratology* 3:105-110, 1981.

Rosenblatt, J.S.; Siegel, H.I.; and Mayer, A.D. Progress in the study of maternal behavior in the rat: Hormonal, nonhormonal, sensory, and developmental aspects. *Advances in the Study of Behavior* 10:226-311, 1979.

Rosett, H.L. A clinical perspective of the fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research* 4:119-122, 1980.

Rosett, H.L., and Weiner, L. *Alcohol and the Fetus: A Clinical Perspective*. New York: Oxford University Press, 1984.

Rosett, H.L.; Weiner, L.; Lee, A.; Zuckerman, B.; Dooling, E.; and Oppenheimer, E. Patterns of alcohol consumption and fetal development. *Gynecology* 61:539-546, 1983.

Schwegler, H.; Lipp, H.-P.; Van der Loos, H.; and Buselmaier, W. Individual hippocampal mossy fiber distribution in mice correlates with two-way avoidance performance. *Science* 214:817-819, 1981.

Shimada, M.; Abe, Y.; Yamano, T.; Ohta, S.; Yamazaki, S.; and Ohya, N. The pathogenesis of abnormal cytoarchitecture in the cerebral cortex and hippocampus of the mouse treated transplacentally with cytosine arabinoside. *Acta Neuropathologica* 58:159-167, 1982.

Sokol, R.J. Alcohol and abnormal outcomes of pregnancy. *Canadian Medical Association Journal* 125:143-148, 1981.

Sokol, R.J. Alcohol and abnormal outcomes of pregnancy. *Substance and Alcohol Actions/Misuse* 3:183-186, 1982.

Sokol, R.J.; Ager, J.; Martier, S.; Debanne, S.; Ernhart, C.; Kuzma, J.; and Miller, S.I. Significant determinants of susceptibility to alcohol teratogenicity. *Annals of the New York Academy of Sciences*. In press.

Sokol, R.J.; Miller, S.I.; and Reed, G. Alcohol abuse during pregnancy: An epidemiological study. *Alcoholism: Clinical and Experimental Research* 4:135-145, 1980.

Stock, D.L.; Streissguth, A.P.; and Martin, D.C. Neonatal sucking as an outcome variable: Comparison of quantitative and clinical assessments. *Early Human Development* 10:273-278, 1985.

Streissguth, A.P.; Barr, H.M.; and Martin, D.C. Alcohol exposure in utero and functional deficits in children during the first four years of life. In: *Mechanisms of Alcohol Damage in utero*. CIBA Foundation Symposium No. 105. London: Pitman Publishing Ltd., 1984, pp. 176-196.

Streissguth, A.P.; Barr, H.M.; Martin, D.C.; and Herman, C.S. Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant development at 8 months. *Alcoholism: Clinical and Experimental Research* 4:152-164, 1980.

Streissguth, A.P.; Barr, H.M.; Sampson, P.D.; Parrish-Johnson, J.C.; Kirchner, G.L.; and Martin, D.C. Attention, distraction, and reaction time at age 7 years and maternal drinking during pregnancy. *Neurobehavioral Toxicology and Teratology*, in press.

Streissguth, A.P.; Clarren, S.K.; and Jones, K.L. Natural history of the fetal alcohol syndrome: A 10-year follow-up of eleven patients. *Lancet* 2:85-91, 1985.

Streissguth, A.P.; Darby, B.L.; Barr, H.M.; Smith, J.R.; and Martin, D.C. Comparison of drinking and smoking patterns during pregnancy over a six-year interval. *American Journal of Obstetrics and Gynecology* 145:716-724, 1983.

Streissguth, A.P.; Herman, C.S.; and Smith, D.W. Intelligence, behavior, and dysmorphogenesis in the fetal alcohol syndrome: A report on 20 patients. *Journal of Pediatrics* 92:363-367, 1978.

Streissguth, A.P.; Landesman-Dwyer, J.C.; Martin, J.C.; and Smith, D.W. Teratogenic effects of alcohol in human and laboratory animals. *Science* 209:353-361, 1980.

Streissguth, A.P.; Martin, D.C.; and Barr, H.M. Maternal alcohol use and neonatal habituation assessed with the Brazelton Scale. *Child Development* 54:1109-1118, 1983.

Streissguth, A.P.; Martin, D.C.; Barr, H.M.; Sandman, B.M.; Kirchner, G.L; and Darby, B.L. Intrauterine alcohol and nicotine exposure: Attention and reaction time in four-year-old children. *Developmental Psychology* 20:533-541, 1984.

Stromland, K. Eyeground malformation in the fetal alcohol syndrome. *Neuropediatrics* 12:97-98, 1981.

Sulik, K.K.; Lauder, J.M.; and Dehart, D.B. Brain malformations in prenatal mice following acute maternal ethanol administration. *International Journal of Developmental Neuroscience* 2:203-214, 1984.

Sullivan, W.C. A note on the influence of maternal inebriety on the offspring. *Journal of Mental Science* 45:489-503, 1899.

Surgeon General's advisory on alcohol and pregnancy. FDA Drug Bulletin 11:9-10, 1981.

Thadani, P.V., and Schanberg, S.N. Effects of maternal ethanol ingestion on serum growth hormone in the developing rat. *Neuropharmacology* 18:821-826, 1979.

Ulleland, C.N. The offspring of alcoholic mothers. *Annals of the New York Academy of Sciences* 21:167-169, 1972.

U.S. Department of the Treasury and U.S. Department of Health and Human Services. *On Health Hazards Associated with Alcohol and Methods to Inform the General Public of These Hazards*. Washington, DC: U.S. Government Printing Office, 1980.

Vane, J.R. Inhibitors of prostaglandin, prostacyclin, and thromboxane synthesis. *Advances in Prostaglandin and Thromboxane Research* 4:27-44, 1978.

Van Dongen, P.A.M. The human locus coeruleus in neurology and psychiatry. *Progress in Neurobiology* 17:97-139, 1981.

Van Thiel, D.H.; Gavaler, J.S.; and Lester, R. Alcohol-induced ovarian failure in the rat. *Journal of Clinical Investigation* 61:524-632, 1978.

Van Thiel, D.H.; Gavaler, J.S.; and Lester, R. Ethanol: A gonadal toxin in the female. *Drug and Alcohol Dependence* 2:373-380, 1977.

Van Thiel, D.H.; Gavaler, J.S.; Lester, R.; and Goodman, M.D. Alcohol-induced testicular atrophy: An experimental model for hypogonadism occurring in chronic alcoholic men. *Gastroenterology* 69:326-332, 1975.

Volk, B.; Maletz, J.; Tiedemann, M.; Mall, G.; Klein, C.; and Berlet, H.H. Impaired maturation of Purkinje cells in the fetal alcohol syndrome of the rat: Light and electron microscopic investigations. *Acta Neuropathologica* 54:19-29, 1981.

Warner, R.H., and Rosett, H.L. The effects of drinking on offspring: An historical survey of the American and British literature. *Journal of Studies on Alcohol* 36:1395-1420, 1975.

West, J.R., and Hamre, K.M. Effects of alcohol exposure during different periods of development: Changes in hippocampal mossy fibers. *Developmental Brain Research* 17:280-284, 1985.

West, J.R., and Hodges-Savola, C.A. Permanent hippocampal mossy fiber hyperdevelopment following prenatal ethanol exposure. *Neurobehavioral Toxicology and Teratology* 5:139-150, 1982.

West, J.R.; Dewey, S.L.; and Cassell, M.D. Prenatal ethanol exposure alters the post-lesion reorganization (sprouting) of acetylcholinesterase staining in the dentate gyrus of adult rats. *Developmental Brain Research* 12:83-95, 1984.

West, J.R.; Hodges, A.; and Black, A.C., Jr. Abnormal neuronal connections in the rat brain following prenatal exposure to ethanol. *Alcoholism: Clinical and Experimental Research* 5:171, 1981a.

West, J.R.; Hodges, A.; and Black, A.C., Jr. Prenatal exposure to ethanol alters the organization of hippocampal mossy fibers in rats. *Science* 211:957-959, 1981b.

Zierler, S., and Rothman, K. "Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy." Paper presented at the 18th annual meeting of the Society for Epidemiologic Research, Chapel Hill, NC, June 1985.

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